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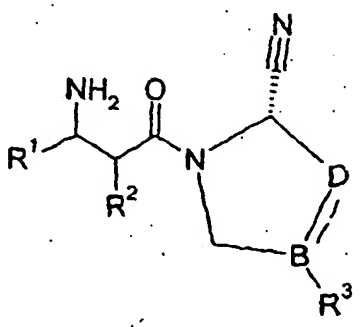
(54) Title: 2-CYANOPYRROLES AND THEIR ANALOGUES AS DDP-IV INHIBITORS



(I)

(57) Abstract: The present invention relates to therapeutically active and selective inhibitors of the enzyme DPP-IV having the formula I: (I) The invention furthermore relates to pharmaceutical compositions comprising the compounds and the use of such compounds for the manufacture of medicaments for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity.

2-CYANOPYRROLES AND THEIR ANALOGUES AS DDP-IV INHIBITORS

FIELD OF THE INVENTION

The present invention relates to new therapeutically active and selective inhibitors of the enzyme DPP-IV. The invention furthermore relates to pharmaceutical compositions comprising the compounds and the use of such compounds for the manufacture of medicaments for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity, as well as methods for treating such diseases.

BACKGROUND OF THE INVENTION

Dipeptidyl peptidase-IV (DPP-IV), a serine protease belonging to the group of post-proline/alanine cleaving amino-dipeptidases, specifically removes the two N-terminal amino acids from proteins having proline or alanine in position 2.

Although the physiological role of DPP-IV has not been completely established, it is believed to play an important role in neuropeptide metabolism, T-cell activation, gastric ulceration, functional dyspepsia, obesity, appetite regulation, impaired fasting glucose (IFG) and diabetes.

DPP-IV has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones Glucagon like peptide-1 (GLP-1) and Gastric inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms; removal of their two N-terminal amino acids inactivates them.

In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, therefore, improved glucose tolerance. Therefore, such inhibitors have been proposed for the treatment of patients with Type 2 diabetes, a disease characterised by decreased glucose tolerance. (Holst, J. J.; Deacon, C. F. Diabetes 47 (1998) 1663-70)

Diabetic dyslipidemia is characterized by multiple lipoprotein defects, including moderately high serum levels of cholesterol and triglycerides, small LDL particles, and low levels of HDL cholesterol. The results of recent clinical trials reveal beneficial effects of cholesterol-lowering therapy in diabetic and non-diabetic patients, thus supporting increased emphasis on treatment of diabetic dyslipidemia. The National Cholesterol Education Program's Adult Treatment Panel II advocated this need for intensive treatment of diabetic dyslipidemia.

Obesity is a well-known risk factor for the development of many very common diseases such as atherosclerosis, hypertension and diabetes. The incidence of obese people and thereby also these diseases is increasing throughout the entire industrialised world. Except for

exercise, diet and food restriction no convincing pharmacological treatment for reducing body weight effectively and acceptably currently exist. However, due to its indirect but important effect as a risk factor in mortal and common diseases it will be important to find treatment for obesity or appetite regulation. Even mild obesity increases the risk for premature death, diabetes, hypertension, atherosclerosis, gallbladder disease and certain types of cancer. In the industrialised western world the prevalence of obesity has increased significantly in the past few decades. Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority.

At present a variety of techniques are available to effect initial weight loss. Unfortunately, initial weight loss is not an optimal therapeutic goal. Rather, the problem is that most obese patients eventually regain their weight. An effective means to establish and/or sustain weight loss is the major challenge in the treatment of obesity today.

Inhibitors of DPP-IV have previously been disclosed in WO 95/15309 (Ferring B.V.), WO 98/19998, WO 00/34241, US 6124305 (Novartis AG), WO 03/00180 (Merck & Co.), and WO 02/38541 (Taisho Pharmaceutical Co.). However, there is still a need for compounds with improved pharmacological properties.

SUMMARY OF THE INVENTION

The present invention provides novel potent and selective inhibitors of DPP-IV of formula I, that are effective in treating conditions that may be regulated or normalised via inhibition of DPP-IV. The invention also concerns methods for preparing the compounds, pharmaceutical compositions comprising the compounds, a method of inhibiting DPP-IV comprising administering to a patient in need of such treatment a therapeutically effective amount thereof, the compounds for use as a pharmaceutical, and their use in a process for the preparation of a medicament for treating a condition which may be regulated or normalised via inhibition of DPP-IV.

DEFINITIONS

The term " DPP-IV" as used herein is intended to mean Dipeptidyl peptidase IV (EC 3.4.14.5; DPP-IV), also known as CD26. DPP-IV cleaves a dipeptide from the N terminus of a polypeptide chain containing a proline or alanine residue in the penultimate position.

The term "treatment" is defined as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of

the present invention to prevent the onset of the symptoms or complications, or alleviating the symptoms or complications, or eliminating the disease, condition, or disorder.

The term "beta cell degeneration" is intended to mean loss of beta cell function, beta cell dysfunction, and death of beta cells, such as necrosis or apoptosis of beta cells.

The term "C_{1-15} alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having from 1-15 carbon atoms such as but not limited to e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec. Butyl, isobutyl, tert. Butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 4-methylpentyl, neopentyl, 2,2-dimethylpropyl and the like.

The term "C_{2-15}-alkenyl" used herein, alone or in combination, refers to a straight or branched, unsaturated hydrocarbon chain having from 2-15 carbon atoms and at least one double bond such as but not limited to vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl and the like.

The term "C_{2-15} alkynyl" as used herein, alone or in combination, refers to an unsaturated hydrocarbon chain having from 2-15 carbon atoms and at least one triple bond such as but not limited to -C≡CH, -C≡CCH$_3$, -CH$_2$C≡CH, -CH$_2$-CH$_2$-C≡CH, -CH(CH$_3$)C≡CH and the like.

The term "C_{1-10}-alkoxy" as used herein, alone or in combination is intended to include those C_1-C_{10}-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "C_{3-15}-cycloalkyl" as used herein refers to a radical of one or more saturated cyclic hydrocarbon having from 3-15 carbon atoms, including bi- or polycyclic hydrocarbon systems, non-limiting examples of C_3-C_{15}-cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl and the like.

The term "spiro-C_{3-10}-cycloalkyl" as used herein refers to a C_{3-10}-cycloalkyl radical as defined above having from 3 to 10 carbon atoms connected to the group to which it is attached through a common carbon atom.

The term "C_{5-15}-cycloalkenyl" as used herein refers to a radical of one or more cyclic hydrocarbon having at least one double bond having from 5-15 carbon atoms, including bi- or polycyclic hydrocarbon systems having at least one double bond, non-limiting examples of C_{5-15}-cycloalkenyl are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-

cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl, bicyclo[2.2.1]hept-5-en-2-yl and the like.

The term "halogen" as used herein refers to fluoro, chloro, bromo, and iodo.

The term "C_{5-10}-cycloheteroalkyl" as used herein represents a non-aromatic 5 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "C_{5-10}-cycloheteroalkenyl" as used herein represents a non-aromatic 5 to 10 membered ring having at least one double bond and containing one or more heteroatoms selected from nitrogen, oxygen and sulphur.

The term "aryl" as used herein is intended to include carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, carbocyclic, aromatic ring systems. Representative examples are phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, azulenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

The term "heteroaryl" as used herein is intended to include aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

The term "ArG1" as used herein is intended to include an aryl radical, where aryl is as defined above but limited to phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, and azulenyl.

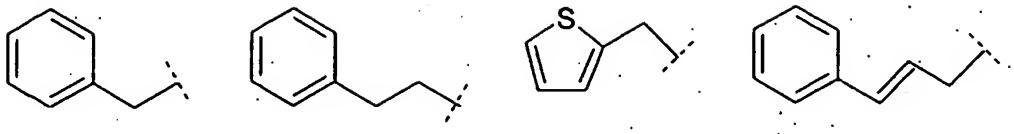
The term "ArG2" as used herein is intended to include an aryl radical, where aryl is as defined above but limited to phenyl, biphenylyl, naphthyl, fluorenyl, and indenyl.

The term "Het1" as used herein is intended to include a heteroaryl radical, where heteroaryl is as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl.

The term "Het2" as used herein is intended to include a heteroaryl radical, where heteroaryl is as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl.

The term "Het3" as used herein is intended to include a heteroaryl radical, where heteroaryl is as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyridyl, tetrazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl.

"Aryl-C_{1-10}-alkyl", "heteroaryl-C_{1-10}-alkyl", "aryl-C_{2-10}-alkenyl", Aryl-C_{1-10}-alkoxy etc. is intended to mean C_{1-10}-alkyl, C_{1-10}-alkoxy or C_{2-10}-alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:

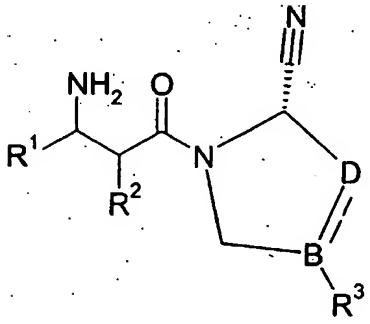


The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different. Furthermore, when the groups are made up of two distinct parts, e.g. aryl-C_{1-10}-alkyl, where the parts are aryl and C_{1-10}-alkyl respectively, either or both of the parts may be substituted with one or more of the substituents specified which may be the same or different.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula I



Formula I

wherein

B and D are independently selected from carbon, nitrogen, oxygen, or sulphur.

The bond between B and D may be a single bond, and when one or both of B and D is not carbon, the bond connecting B and D may be a double bond.

R^1 is

- C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{2-15}-alkynyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, aryl-C_{2-10}-alkenyl, or heteroaryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4

- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8;

R^2 is hydrogen, C_{1-10}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, spiro-C_{3-10}-cycloalkyl, aryl-C_{1-10}-alkyl, -C(=O)-C_{1-10}-alkyl, -C(=O)-aryl, -C(=O)-heteroaryl, each optionally substituted with one or more substituents independently selected from R^4;

When R^2 is hydrogen R^1 may also be hydrogen;

R^3 is hydrogen, hydroxy, halogen, C_{1-10}-alkoxy, C_{1-10}-alkyl, aryl, aryloxy, aryl-C_{1-10}-alkoxy, heteroaryl, cyano, cyanoalkyl, and $COOR^2$;

R^4 is halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, perhalomethyl, perhaloethyl, cyano, phenyl, $COOR^5$, $CONR^5R^6$, $O(CO)R^5$, C_{1-10}-alkoxy, aryl-C_{1-10}-alkoxy, SR^5, SO_3R^5, NR^5R^6, $NHCOR^5$, or COR^5;

R^5 and R^6 are independently selected from hydrogen, C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, or aryl;

R^5 and R^6 together may form a C_{3-7}-alkylene bridge that optionally may be substituted with one or more R^7 independently;

R^7 is independently selected from cyano, halogen, hydroxy, C_{1-10}-alkyl, C_{1-10}-alkoxy, aryl, and heteroaryl;

R^8 is halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, perhalomethyl, perhaloethyl, cyano, phenyl, $COOR^9$, $CONR^{10}R^{11}$, $O(CO)R^9$, C_{1-10}-alkoxy, -C_{1-10}-alkyl-C(O)-R^9, -C_{1-10}-alkyl-C(O)-R^9, aryl-C_{1-10}-alkoxy, SR^9, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, SO_3R^9, $NR^{10}R^{11}$, $NHCOR^9$, or COR^9;

R^9 is C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{2-15}-alkynyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, aryl-C_{2-10}-alkenyl, heteroaryl-C_{1-10}-alkyl, C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12};

R^{10} and R^{11} are independently selected from hydrogen, C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, or aryl;

R^{12} is independently selected from halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, perhalomethyl, perhaloethyl, cyano, phenyl, COOH, $CONH_2$, C_{1-10}-alkoxy, aryl-C_{1-10}-alkoxy, SH, or NH_2;

R^1 and R^2 together may form a C_{3-7}-alkylene or C_{3-7}-alkenylene bridge to which is fused a phenyl or a heteroaryl ring;

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In one embodiment B is carbon, nitrogen or sulphur.

In one embodiment B is carbon or nitrogen.

In one embodiment B is carbon.

In one embodiment D is carbon, nitrogen or sulphur.

In one embodiment D is carbon or nitrogen.

In one embodiment D is carbon.

In one embodiment R^1 is

- C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, aryl-C_{2-10}-alkenyl, or heteroaryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

In one embodiment R^1 is

- C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, or aryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

In one embodiment R^1 is

- C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1, heteroaryl, or ArG1-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

In one embodiment R^1 is

- C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, heteroaryl, or ArG1-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4.
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

In one embodiment R^1 is C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4, or C_{5-10}-cycloheteroalkyl optionally substituted with one or more substituents independently selected from R^8.

In one embodiment R^1 is cyclopentyl, cyclohexyl, cyclohexyl, bicyclo[2.2.1]heptyl, adamantyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-5-enyl, benzyl, each optionally substituted with one or more substituents independently selected from R^4, or pyrrolyl, piperidinyl, or hexahydroazepinyl, each optionally substituted with one or more substituents independently selected from R^8.

In one embodiment R^1 is 3-piperidinyl or 4-piperidinyl each optionally substituted by R^8.

In one embodiment R^1 is 3-piperidinyl or 4-piperidinyl each optionally substituted at the nitrogen atom by R^8.

In one embodiment heteroaryl is Het1.

In one embodiment heteroaryl is Het2.

In one embodiment heteroaryl is Het3.

In one embodiment R^2 is hydrogen, C_{1-10}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, aryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4.

In one embodiment R^2 is hydrogen, C_{1-10}-alkyl, C_{3-10}-cycloalkyl, phenyl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4.

In one embodiment R^2 is hydrogen.

In one embodiment R^1 and R^2 together form a C_{3-7}-alkylene or C_{3-7}-alkenylene bridge to which is fused a phenyl ring.

In one embodiment R^3 is hydrogen, hydroxy, halogen, C_{1-10}-alkoxy, C_{1-10}-alkyl, aryl, aryloxy, or aryl-C_{1-10}-alkoxy.

In one embodiment R^3 is hydrogen, hydroxy, halogen, C_{1-10}-alkyl, or aryl-C_{1-10}-alkoxy.

In one embodiment R^3 is hydrogen or aryl-C_{1-10}-alkoxy.

In one embodiment R^3 is hydrogen.

In one embodiment R^4 is halogen, C_{1-5}-alkyl, hydroxy, OCF_3, $OCHF_2$, phenyl, $COOR^5$, $CONR^5R^6$, $O(CO)R^5$, C_{1-10}-alkoxy, aryl-C_{1-10}-alkoxy, NR^5R^6, or COR^5.

In one embodiment R^4 is halogen, C_{1-5}-alkyl, hydroxy, phenyl, $COOR^5$, $CONR^5R^6$, $O(CO)R^5$, NR^5R^6, or COR^5.

In one embodiment R^4 is halogen, C_{1-5}-alkyl, $COOR^5$, $CONR^5R^6$, NR^5R^6, or COR^5.

In one embodiment R^4 is halogen, C_{1-5}-alkyl, $COOR^5$, or $CONR^5R^6$.

In one embodiment R^5 is hydrogen or C_{1-10}-alkyl.

In one embodiment R^6 is hydrogen or C_{1-10}-alkyl.

In one embodiment R^5 and R^6 together form a C_{3-7}-alkylene bridge optionally substituted with one or more R^7.

In one embodiment R^7 is cyano, halogen, hydroxy, C_{1-10}-alkyl, or C_{1-10}-alkoxy.

In one embodiment R^7 is cyano, halogen, hydroxy, or C_{1-10}-alkyl.

In one embodiment R^7 is cyano or halogen.

In one embodiment R^7 is cyano.

In one embodiment R^8 is halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, cyano, phenyl, $COOR^9$, $CONR^{10}R^{11}$, $O(CO)R^9$, C_{1-10}-alkoxy, -C_{1-10}-alkyl-C(O)-R^9, -C_{1-10}-alkyl-C(O)-R^9, SR^9, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, $NR^{10}R^{11}$, or COR^9.

In one embodiment R^8 is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, $COOR^9$, $O(CO)R^9$, C_{1-10}-alkoxy, -C_{1-10}-alkyl-C(O)-R^9, -C_{1-10}-alkyl-C(O)-R^9, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, $NR^{10}R^{11}$, or COR^9.

In one embodiment R^8 is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, $COOR^9$, $O(CO)R^9$, C_{1-10}-alkoxy, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, $NR^{10}R^{11}$, or COR^9.

In one embodiment R^8 is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, $NR^{10}R^{11}$, or COR^9.

In one embodiment R^9 is C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1, Het1, ArG1-C_{1-10}-alkyl, or C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12}.

In one embodiment R^9 is C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1, or C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12}.

In one embodiment R^9 is C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, phenyl or C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12}.

In one embodiment R^{10} and R^{11} are independently selected from hydrogen, C_{1-10}-alkyl, or phenyl.

In one embodiment R^{10} and R^{11} are independently selected from hydrogen or methyl.

In one embodiment R^{12} is halogen, C_{1-5}-alkyl, hydroxy, OCF_3, $OCHF_2$, cyano, phenyl, COOH, $CONH_2$, C_{1-10}-alkoxy, SH, or NH_2.

In one embodiment R^{12} is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, COOH, SH, or NH_2.

In another aspect the invention provides the use of any of the compounds of the invention as a pharmaceutical composition.

In another aspect the invention provides a pharmaceutical composition comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

In one embodiment the invention provides such a pharmaceutical composition in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound of the invention.

In one embodiment the composition furthermore comprises an inhibitor of neutral endopeptidase (NEP).

In another aspect the invention provides the use of a compound of the general formula (I) or a diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of disorders and diseases in which an inhibition of DPP-IV has a beneficial effect.

In one embodiment the invention provides the use of a compound of the invention for the preparation of a pharmaceutical composition for the treatment of IGT.

In one embodiment the use of a compound of the invention for the preparation of a pharmaceutical composition for the treatment of type 2 diabetes.

In one embodiment the invention provides the use of a compound of the invention for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to type 2 diabetes.

In one embodiment the invention provides the use of a compound of the invention for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

In one embodiment the invention provides the use as described above wherein the pharmaceutical composition furthermore comprises an inhibitor of neutral endopeptidase (NEP).

In another aspect the invention provides a method for the treatment of disorders or diseases in which an inhibition of DPP-IV has a beneficial effect, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention or a pharmaceutical composition as described above.

In one embodiment the invention provides the above method wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

COMBINATION TREATMENT

The invention furthermore relates to treatment of a patient in which the compounds of the invention are combined with another form of treatment.

In one aspect of the invention, treatment of a patient with the compounds of the invention are combined with diet and/or exercise.

In another aspect of the invention the compounds of the invention are administered in combination with one or more further active substances in any suitable ratios. Such further active substances may e.g. be selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment of complications resulting from or associated with diabetes and agents for the treatment of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the compounds of the invention may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, MC3 (melanocortin 3) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors such as fluoxetine, seroxat or citalopram, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators, TR β agonists, AGRP (Agouti related protein)

inhibitors, H3 histamine antagonists, opioid antagonists (such as naltrexone), exendin-4, GLP-1 and ciliary neurotrophic factor.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

In still another embodiment the antiobesity agent is phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate or ecopipam.

The orally active hypoglycemic agents comprise imidazolines, sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers, insulin secretagogues such as glimepride, α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the β-cells e.g. potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, or mitiglinide, or a potassium channel blocker, such as BTS-67582, nateglinide, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, GLP-1 agonists such as those disclosed in WO 00/42026 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists, such as ALRT-268, LG-1268 or LG-1069.

In a further embodiment of the invention compounds of the invention are administered in combination with a sulphonylurea e.g. tolbutamide, chlorpropamide, tolazamide, glibenclamide, glipizide, glimepiride, glicazide or glyburide.

In another embodiment of the invention the compounds of the invention are administered in combination with a biguanide, e.g. metformin.

In yet another embodiment of the invention the compounds of the invention are administered in combination with a meglitinide e.g. repaglinide or nateglinide.

In still another embodiment of the invention the compounds of the invention are administered in combination with a thiazolidinedione insulin sensitizer, e.g. troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T 174 or the compounds disclosed in WO 97/41097, WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292 (Dr. Reddy's Research Foundation), which are incorporated herein by reference.

In still another embodiment of the invention the pharmaceutical preparation of the invention may be administered in combination with an insulin sensitizer, e.g. such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516 or the compounds disclosed in WO 99/19313, WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 (Dr. Reddy's Research Foundation) and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 00/63196, WO 00/63209, WO 00/63190 and WO 00/63189 (Novo Nordisk A/S), which are incorporated herein by reference.

In a further embodiment of the invention the compounds of the invention are administered in combination with an α-glucosidase inhibitor, e.g. voglibose, emiglitate, miglitol or acarbose.

In another embodiment of the invention the compounds of the invention are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells, e.g. tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In yet another embodiment of the invention the pharmaceutical preparation of the invention may be administered in combination with nateglinide.

In still another embodiment of the invention the compounds of the invention are administered in combination with an antilipidemic agent, e.g. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In another aspect of the invention, the compounds of the invention are administered in combination with more than one of the above-mentioned compounds, e.g. in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; acarbose and metformin; a sulphonylurea, metformin and troglitazone; metformin and a sulphonylurea; etc.

Furthermore, the compounds of the invention may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil,

prazosin and terazosin. The compounds of the invention may also be combined with NEP (neutral endopeptidase) inhibitors such as candoxatril.

Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The compounds of the invention may also be administered in combination with one or more antidiabetics. Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference as well as orally active hypoglycemic agents.

In one preferred embodiment the antidiabetic is insulin or an analogue thereof or a derivative thereof. More preferably the antidiabetic is human insulin or an analogue thereof or a derivative thereof. However, porcine insulin is also an insulin species, which may be employed with the present invention. Preferably, porcine insulin is highly purified naturally produced porcine insulin.

Human insulin could be naturally produced insulin, or human insulin recombinantly produced. Recombinant human insulin may be produced in any suitable host cell for example the host cells may be bacterial, fungal (including yeast), insect, animal or plant cells. Preferably, the host cells are yeast cells or bacterial cells such as for example *E. coli*.

In one embodiment the analogue of human insulin is a rapid-acting analogue. For example the analogue may be selected from the group consisting of AspB28 human insulin and LysB28ProB29 human insulin.

In one embodiment the derivative is human insulin or an analogue thereof containing a C_6 to C_{40} lipophilic substituent in position B29. The derivative may be selected from the group consisting of B29-N^{ε}-myristoyl-des(B30) human insulin, B29-N^{ε}-palmitoyl-des(B30) human insulin, B29-N^{ε}-myristoyl human insulin, B29-N^{ε}-palmitoyl human insulin, B28-N^{ε}-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N^{ε}-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N^{ε}-myristoyl-$Thr^{B29}Lys^{B30}$ human insulin, B30-N^{ε}-palmitoyl-$Thr^{B29}Lys^{B30}$ human insulin, B29-N^{ε}-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^{ε}-(ω-carboxyheptadecanoyl) human insulin.

In addition, a variety of different insulin compositions are antidiabetics which should also be considered to fall within the scope of the present invention. For example this includes regular insulin, Semilente® insulin, isophane insulin, insulin zinc suspensions, protamine zinc insulin, and Ultralente® insulin.

Isophane insulin is an isophane mixture of protamine and insulin, wherein a ratio of protamine to insulin is mixed, which is equal to the ratio in a solution made by mixing equal parts of a solution of the two in which all the protamine precipitates and a solution of the two in which all the insulin precipitates.

In one embodiment the insulin compositions to be administered in combination with a compound of the invention are characterised by a fast onset of action, while in other embodiments the insulin compositions have a relatively slow onset but show a more or less prolonged action. Fast acting insulin compositions are usually solutions of insulin, while retarded acting insulin compositions can be suspensions containing insulin in crystalline and/or amorphous form precipitated by addition of zinc salts alone or by addition of protamine or by a combination of both. In addition, some compositions have both a fast onset of action and a more prolonged action. Such a composition may be an insulin solution wherein protamine insulin crystals are suspended. Furthermore, compositions obtained by mixing an insulin solution with a suspension composition in the desired ratio are useful with the present invention.

The compounds of the present invention may be administered in combination with one or more compositions comprising analogues and/or derivatives of human insulin. Thus, the compounds of the present invention may be administered in combination with one or more insulin compositions comprising one or more fast-acting analogues of human insulin, in particular analogues wherein the amino acid residue at position B28 is Asp, Lys, Leu, Val or Ala and the amino acid residue at position B29 is Lys or Pro; or des(B28-B30), des(B27) or des(B30) human insulin. The insulin analogue may be selected from analogues of human insulin wherein the amino acid residue at position B28 is Asp or Lys, and the amino acid residue at position B29 is Lys or Pro, e.g. Asp_{B28} human insulin and Lys_{B28} Pro_{B29} human insulin.

In another embodiment the compounds of the present invention may be administered in combination with one or more insulin compositions comprising an insulin derivative having a

protracted profile of action, such an insulin having one or more lipophilic substituents. Lipophilic insulins may be acylated insulins, including those described in WO 95/07931, e.g. human insulin derivatives wherein the ε-amino group of Lys_{B29} contains an acyl substituent which comprises at least 6 carbon atoms.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the invention of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable basic addition salt or prodrug or hydrate thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier that may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatine, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene,

hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound of the invention which inhibits the enzymatic activity of DPP-IV to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of the invention which inhibits the enzymatic activity of DPP-IV, dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that may be prepared by conventional tabletting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	250 mg

Colloidal silicon dioxide (Aerosil)®	1.5 mg
Cellulose, microcryst. (Avicel)®	70 mg
Modified cellulose gum (Ac-Di-Sol)®	7.5 mg
Magnesium stearate	Ad.

Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of the various diseases as mentioned above, e.g. type II diabetes, IGT, IFG, obesity, appetite regulation or as a blood glucose lowering agent, and especially type II diabetes. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day may be used. A most preferable dosage is about 0.5 mg to about 250 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.05 mg to about 1000 mg, preferably from about 0.5 mg to about 250 mg of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

The invention also encompasses prodrugs of a compound of the invention which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a compound of the invention that are readily convertible in vivo into a compound of the

invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of a compound of the invention.

EXAMPLES

The following general synthesis methods can be used to prepare the compounds of the present invention.

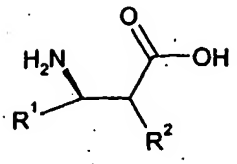
Abbreviations

Bn	Benzyl	HOBt	1-Hydroxybenzotriazole
Boc	tert-Butyloxycarbonyl	mesylate	Methanesulphonate
BSA	bis Trimethylsilylacetamide	NMP	N-Methylpyrrolidone
DCM	Dichloromethane	PS	Polystyrene
DCP	1,2-Dichloropropane	PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
DIEA	Diisopropylethylamine	TFAA	Trifluoroacetic anhydride
DMAP	4-Dimethylaminopyridine	TFA	Trifluoroacetic acid
DMF	Dimethylformamide	THF	Tetrahydrofurane
DMSO	Dimethylsulfoxide	tosylate	4-Methylbenzenesulphonate
EDAC	1-Ethyl-3-(3-dimethyl-aminopropyl)carbodiimide	triflate	Trifluoromethylsulphonate
Fmoc	9-Fluorenylmethyloxycarbonyl	trityl	Triphenylmethyl
HOAt	1-Hydroxy-7-azabenzotriazole	Z	Benzyloxycarbonyl

General synthesis method (C1)

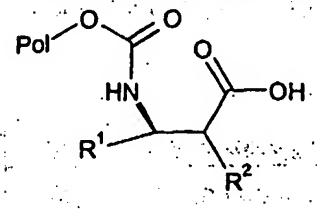
Step C1.1

Reacting a beta amino acid of formula C1,



Formula C1

wherein R^1 and R^2 have the meaning described above, with a p-nitrophenyl carbonate Wang resin - commercially available from Novabiochem – to give a compound of formula C2

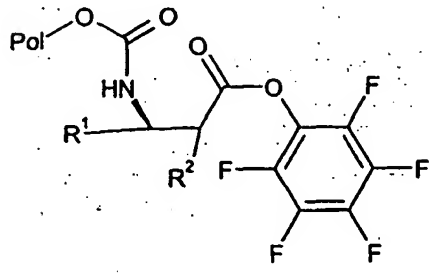


formula C2

wherein R^1 and R^2, have the meaning described above, and Pol is the Wang resin

Step C1.2

Reacting a compound of formula C2 with pentafluorophenyl trifluoroacetate to give a compound of formula C3

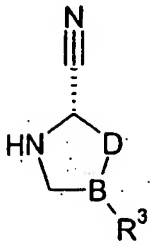


formula C3

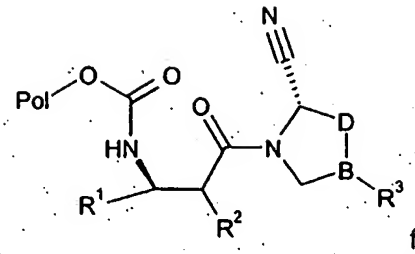
wherein R^1 and R^2, have the meaning described above and Pol is the Wang resin

Step C1.3

Reacting a compound of formula C3 with a compound of formula C4 to give a compound of formula C5



formula C4 and



formula C5

wherein B, D, R^1, R^2, and R^3, have the meaning described above and Pol is the Wang resin.

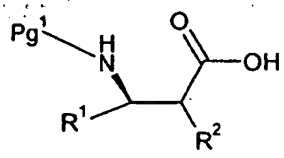
Step C1.4

Liberating a compound of formula C5 from the resin by treatment with an acid such as TFA, to give a compound of formula I, wherein B, C, R^1, R^2, and R^3 have the meaning described above.

General synthesis method (C2)

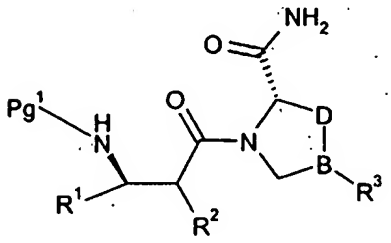
Step C2.1

Reacting a suitably N-protected beta amino acid of formula C6,



Formula C6

wherein R^1 and R^2 have the meaning described above, and the N-protection group Pg^1 is a standard protecting group for use in peptide synthesis, such as the Boc-, Z-, Fmoc, or trityl-group, with a S-Proline amide, using standard conditions for amide bond formation, such as active ester formation (HOBt-esters, HOAt-esters, pentafluorophenyl-esters etc.) via carbodiimide activation, symmetrical anhydride activation, unsymmetrical anhydride formation (e.g. reaction with chloroformate esters), or directly from the anhydrides, to form compounds of formula C7,

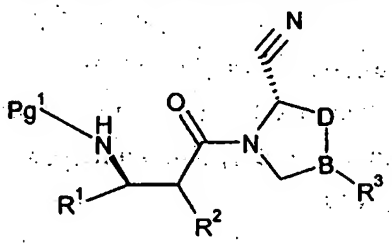


Formula C7

wherein B, D, R^1, R^2, R^3, and Pg^1 have the meaning described above.

Step C2.2

Reacting a suitably protected beta amino acid of formula C7, wherein B, C, R^1, R^2, R^3, and Pg^1 have the meaning described above, with a dehydrating agent, such as phosphorous oxychloride in pyridine or DMF, or trifluoroacetic acid anhydride, or the bromine/triphenylphospine adduct, to give the nitrile product of formula C8



formula C8

wherein B, D, R^1, R^2, R^3, and Pg^1 have the meaning described above.

Step C2.3

Removing the N-protecting group Pg^1 of a compound of formula C8, such as by treatment with acid for the removal of the Boc- or the Trityl group, hydrogenation for removal of the Z-group, or piperidine or similar base treatment for removal of the Fmoc group, to give the compounds of formula I, wherein B, D, R^1, R^2, and, R^3 have the meaning described above.

General synthesis method (C3)

This method is similar to method (CA2) except that in step C3.1 the beta amino acid is reacted with a S-2-Cyanopyrrolidine of formula C4 to give directly a compound of formula C8, wherein B, D, R^1, R^2, R^3, and Pg^1 have the meaning described above, thus avoiding step C2.2. Step C3.3 is identical to step C2.3 in method (C2)

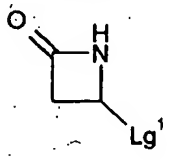
The beta amino acids of formula C6, wherein R^1, R^2, and Pg^1 have the meaning described above, are either commercially available from general chemistry vendors such as Aldrich, Lancaster, Merck, or Maybridge, or from vendors specialised in amino acids and peptides, such as Bachem (Schwitzerland), Novabiochem (Germany), RSP (Ma, USA), Peptech (Ma, USA), Advanced Chemtech. (KY, USA), Anaspec (Ca, USA), or Chirotech (UK), or they can be prepared by a series of reactions well known in the art for making optically pure as well as

racemic beta-amino acids (for a monograph of current beta amino acid synthesis method see "Enantioselective Synthesis of β-Amino Acids, E. Juaristi Ed. Wiley 1997 ISBN 0-471-18627-9"). The racemic beta-amino acids of formula A1 may be separated into the pure enantiomers either by crystallisation with optically active salts, or by chromatography using an enantioselective stationary phase. Furthermore, diastereomeric beta amino acid amides of formula C7, C8 or formula I may be separated into the pure diastereomers by crystallisation or by chromatography.

General synthesis method (D1)

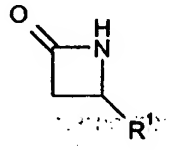
Step D1.1

Reacting a compound of formula D1



formula D1

with a compound of formula Met-R^1, wherein Lg^1 is SO_2-Ph or COMe, R^1 has the meaning described above, and Met is either lithium or magnesium bromide, to give a compound of formula D2

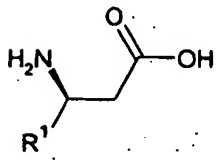


formula D2

wherein R^1 has the meaning described above.

Step D1.2

Hydrolysing a compound of formula D2, using bases such as LiOH, NaOH, KOH, in an alcohol solvent, to give a compound of formula D3



Formula D3

wherein R^1 has the meaning described above.

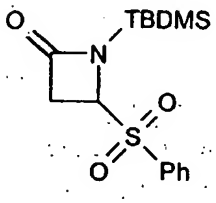
Step D1.2

Reacting a compound of formula D3 with a suitable amine protecting agent, such as Boc-anhydride, Z-chloride, trityl chloride, or a polymer based protecting agent such as described in step C3.1, to give a compound of formula C6, wherein R^2 is H, and R^1 and Pg^1 have the meaning described above.

General synthesis method (D2)

Step D2.1

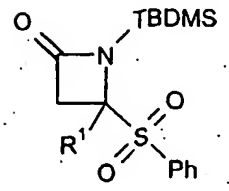
Reacting a compound of formula D1 with tert-Butyl-dimethylsilyl chloride (TBDMS-Chloride) under basic conditions to give a compound of formula D4



Formula D4

Step D2.2

Deprotonating a compound of formula D4 with a strong base such as butyl lithium or lithium diisopropylamine, and reacting the anion with a compound of formula R^1-Lg^2, wherein R^1 has the meaning described above and Lg^2 is a good leaving group such as halogen, tosylate, mesylate, triflate or the like, to give a compound of formula D5



Formula D5

Step D2.3

Reacting a compound of formula D5 through the steps in method D1 to give a compound of formula C1, wherein R^2 is H and R^1 and Pg^1 have the meaning described above

Preparative HPLC (Method A)

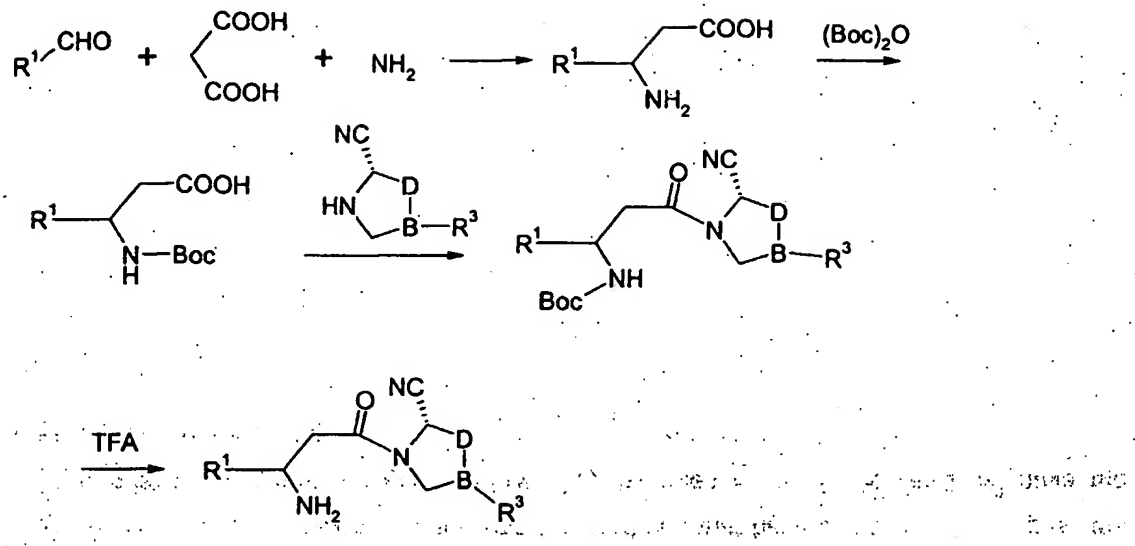
Column: 1.9 x 15 cm Waters XTerra RP-18. Buffer: linear gradient 5 – 95 % in 15 min, MeCN, 0.05 % TFA, flow rate of 15 ml/min. The pooled fractions are either evaporated to dryness *in vacuo*, or evaporated *in vacuo* until the MeCN is removed, and then frozen and freeze dried.

HPLC-MS (Method B)

Column: Waters XTerra MS C-18 X 3 mm id. Buffer: Linear gradient 10 % - 100 % in 7.5 min, acetonitrile, 0.01 % TFA, flow rate 1.5 ml/min. Detection: 210 nm (analog output from diode array detector), MS-detection ionisation mode API-ES, scan 100-1000 amu step 0.1 amu.

The following general procedures describe the methods that have been used to prepare the compounds of the examples given below. The variables B, D, R^1, R^2, and, R^3 have the meaning described above.

General procedure (A)



Step A:

The aldehyde (9.6 mmol), malonic acid (9.6 mmol), and ammonium acetate (19.5 mmol) are allowed to react in 96 % ethanol (2 ml) at 100 °C for 1-6 h or in a micro wave oven for 1-5 min at 150 °C. Upon cooling to room temperature the precipitate is filtered of and washed with ethanol/acetone (1:1) (2 x 1 ml) to give the product.

Step B:

The isolated product from step A (9.6 mmol) is mixed with water (15 ml). A solution of $(Boc)_2O$ (1.1 eq.) in THF (10 ml) and 1 N NaOH (10 ml) are added, and the reaction is stirred for 16 hours. The acidity is adjusted to pH 1-2 with 1 N HCl. The mixture is extracted with ethyl acetate (3 x 10 ml), dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the product, which can be further purified by preparative HPLC (method A).

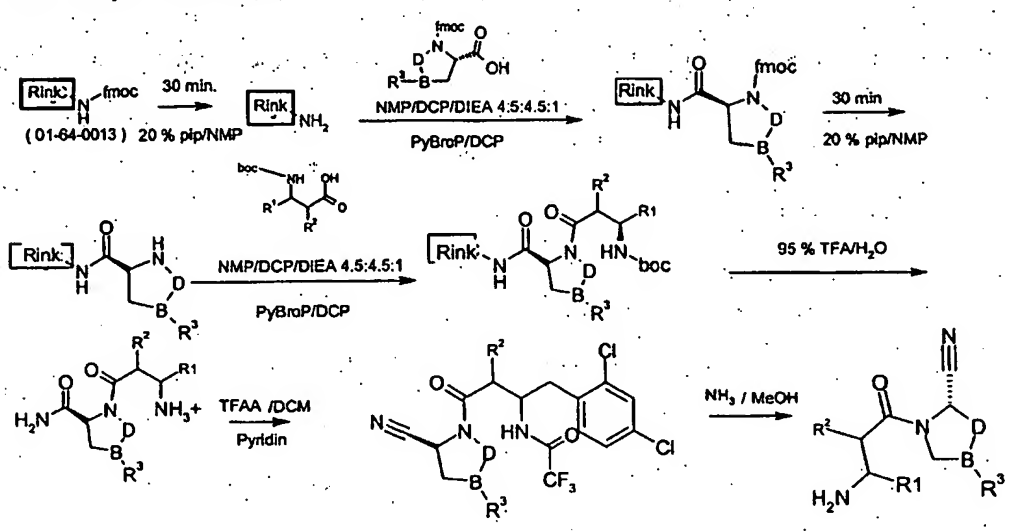
Step C:

The product from step B (1.13 mmol) is dissolved in DCM (6 ml). HOBt (0.19; 1.4 mmol) and EDAC, HCl (0.27 g; 1.4 mmol) are added, followed by (S)-pyrrolidine-2-carbonitrile (0.213 g; 0.10 mmol). The mixture stirred at room temperature for 16 hours and poured into potassium hydrogen sulphate (15 ml 0.5 M in water). After stirring for one hour the organic phase was isolated and washed with 10 % $NaHCO_3$ (2 x 5 ml). The water phase is extracted with DCM (5 ml), and the combined DCM phases are washed with saline (5 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* to give the product, which is further purified by preparative HPLC (method A).

Step D

The product from step D (44 mg, 0.13 mmol) is dissolved in acetonitrile (0.3 ml). Water (0.3 ml) and TFA (0.111 ml) is added, and the reaction mixture is stirred at room temperature for 4 days. The reaction mixture is evaporated *in vacuo* to give the product, which can be further purified by preparative HPLC (method A).

General procedure (B)



Step A:

A shaking vessel was charged with the Rink amide resin (NovaBiochem – loading 0.61 mmol/g – 83 mg, 50 mmol). The resin was briefly swelled in DCM with gentle agitation for 2 h. The Fmoc group was then removed by treatment with 20 % piperidine/NMP (1ml) and shaken for 30 min. The resin was then washed with NMP (6 x 1 ml). To the Rink amine was added a solution of the Fmoc-protected amino acid (400 µmol) in NMP/DCP/DIEA (4.5:4.5:1, 1 ml) followed by a solution of PyBroP (400 µmol) in DCP (0.5 ml). The reaction was shaken for 4 h, filtered and washed with NMP (1 x 1 ml), DCM (1 x 1 ml), and NMP (1 x 1 ml). The Fmoc group was then removed by treatment with 20 % piperidine/NMP (1 ml) and shaken for 30 min. The resin was then washed with NMP (6 x 1 ml).

Step B:

To the resin-bound proline was added a solution of the Boc-protected amino acid (400 µmol) in NMP/DCP/DIEA (4.5:4.5:1) followed by addition of PyBroP (400 µmol) in DCP (0.5 ml). The reaction was shaken for 4 h, filtered and washed with NMP (2 x 1 ml) and DCM (10 x 1 ml). The compound was cleaved from the resin by addition of 95 % TFA in DCM (1.2 ml). The reaction was shaken for 1 h. Further DCM (1 ml) was added and the solution was

drained into a vial and the solvent evaporated in *vacuo* to give the N-substituted pyrrolidinecarboxamide.

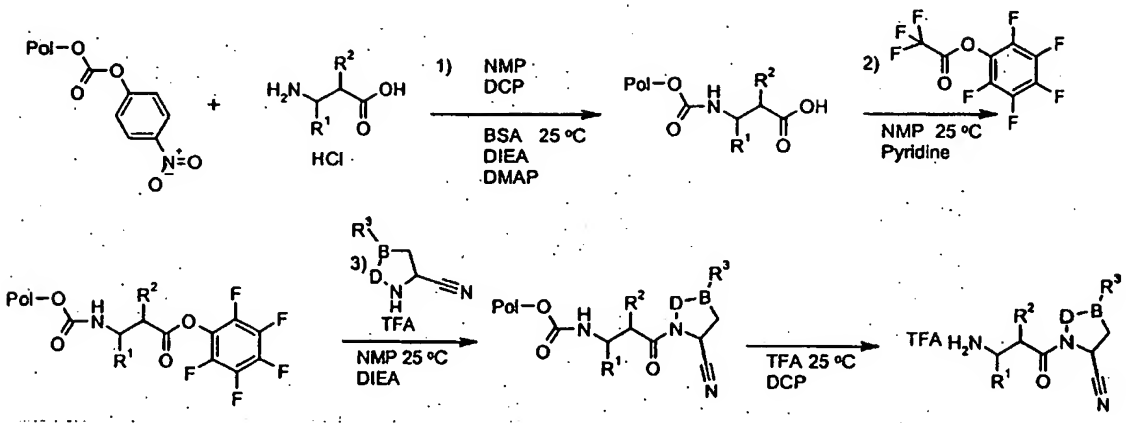
Step C:

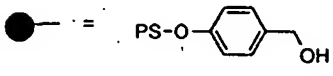
To the product from step B was dissolved in a mixture of TFAA (70 µl) and DCM (430 µl). Pyridine (0.5 ml) was added; the mixture was shaken for 1 h and evaporated in *vacuo* to give the N-substituted trifluoroacetylated pyrrolidinecarbonitrile.

Step D:

The product from step C was dissolved in a saturated ammonia-methanol solution (1 ml) and shaken for 20 h. The solvent was removed in *vacuo* to give the product, which was further purified by preparative HPLC (method A).

General procedure (C)





Wang resin.

PS = Polystyrene

The resin starting material is commercially available from Novabiochem or it can be produced by reacting 4-(hydroxymethyl)phenoxymethyl polystyrene resin with p-nitrophenyl chloroformate in DCM and DIEA. (Dressman, B. A.; Spangle, L. A.: Tetrahedron. Lett. 37 (1996) 937-40).

Step A

The amino acid (100 µmol) and DMAP (50 µmol) is dissolved in a mixture of NMP, DCP, BSA and DIEA (10:10:3:1, 600 µl) and added to a p-nitrophenyl carbonate Wang resin (50

mg) and allowed to react overnight at 25 °C. Upon drainage, the resin is washed with NMP (3x1 ml), a mixture of THF, water and acetic acid (8:1:1, 1ml), THF, (1 ml), methanol (1 ml), N-methyl-2-pyrrolidone (1 ml), methanol (1 ml), N-methyl-2-pyrrolidone (1 ml) and a mixture of N-methyl-2-pyrrolidone and pyridine (9:1, 1 ml).

Step B

Activation of the above resin bound amino acid is carried out by adding a mixture of N-methyl-2-pyrrolidone and pyridine (9:1, 1 ml) and pentafluorophenoltrifluoromethylacetate (80 µl). The mixture is allowed to react at 25 °C for 4h. Then the resin is washed with N-methyl-2-pyrrolidone (2x1 ml).

Step C

2-Cyanopyrrolidine•TFA (250 µmol) was dissolved in NMP and DIEA (5:1, 500 µl), added to the resin bound pentafluorophenyl ester and allowed to react 16h at 25 °C. Upon washing with NMP (4x1 ml) and DCM (10x1ml) the compounds were cleaved from the resin using a mixture of dichloropropane and trifluoroacetic acid (1:1, 1 ml) for 1h at 25 °C. The drained resin was washed with dichloropropane (1 ml) and the combined filtrates were evaporated to give the desired compound that may be further purified by chromatography.

General procedure (D)

Step A:

(Phenylsulfonyl)-2-azetidinone (1.0g; 0.47mmol) is dissolved in dry THF (50 ml) and cooled to –78 °C under N_2. The Grignard reagent (0.95mmol), dissolved in diethyl ether or THF, is added, while keeping the temperature below -60 °C. The reaction mixture is allowed to warm up to 0 °C, kept at 0 °C for 30 min, and - if necessary - further stirred at room temperature under N_2 until finished. A saturated NH_4Cl-water solution (100 ml) is added, and the reaction mixture evaporated *in vacuo*. The residue is extracted with DCM (4x100 ml), dried with $MgSO_4$, filtered, and evaporated *in vacuo* to give the product, which is further purified by preparative HPLC (method A).

Step B:

The isolated product from step A is dissolved in 1N NaOH:EtOH (15:50 ml), and stirred at room temperature for 16 hours. $(Boc)_2O$ (1.3 eq.) is added, and the reaction is further stirred for 16 hours. The EtOH is stripped from the reaction mixture *in vacuo*, further water is added,

and the acidity is adjusted to pH 1-2 with 1 N HCl. The mixture is extracted with DCM (3x100 ml), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the product, which is further purified by preparative HPLC (method A).

Step C:

The product from step B is dissolved in DMF (30 ml). HOBt (0.15; 0.44 mmol), and EDAC (0.126g; 0.66mmol), is added, followed by L-prolinamide (0.050g; 0.44mmol). The mixture stirred at room temperature for 2.5 hours, and evaporated *in vacuo*. The residue is dissolved in DCM (75 ml), and washed with 1N NaOH (50 ml). The NaOH phase is back extracted with DCM (75 ml), and the combined DCM phase is was washed with 5% aqueous acetic acid, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the product, which is further purified by preparative HPLC (method A).

Step D

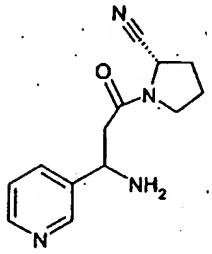
The product from step C is dissolved in DCM (3 ml) and cooled to 0° on ice. Pyridine (0.379 g; 4.79 mmol) is added, and then phosphorous oxychloride (0.196 g; 1.28 mmol) is added slowly. The reaction mixture is stirred at 0° C for 4 hours. The reaction is poured onto ice, and extracted with DCM (2 x 6 ml). The combined DCM phase is washed with saturated $NaHSO_4$ (2 ml), $NaHCO_3$ (2 ml), and brine (2ml), dried with $MgSO_4$, filtered, and evaporated *in vacuo* to give the product, which is further purified by preparative HPLC (method A).

Step E

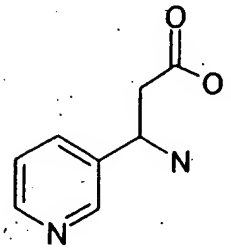
The product from step D is dissolved in acetonitrile (10 ml). TFA (1 ml) is added, and the reaction mixture is stirred at room temperature for 16 hours. The reaction mixture is evaporated *in vacuo* to give the product, which is further purified by preparative HPLC (method A).

Example 1 (General procedure (A))

1-(3-Amino-3-pyridin-3-yl-propionyl)-pyrrolidine-2-carbonitrile (1)

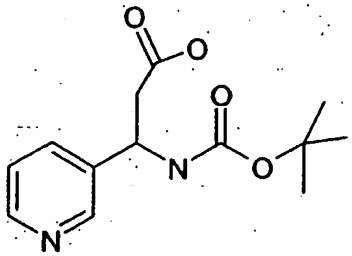


Step A: 3-Amino-3-pyridin-3-yl-propionic acid



^{1}H NMR (CD_3OD): δ 8.66 (d, 1H), 8.56 (dd, 1H), 7.95 (dt, 1H), 7.52 (dd, 1H), 4.64 (m, 1H), 2.75 (m, 2H). HPLC-MS (Method B): m/z: 167 (M+1); Rt = 0.23 min.

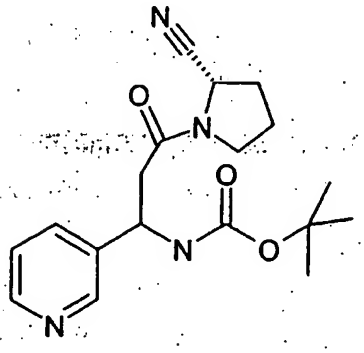
Step B: 3-tert-Butoxycarbonylamino-3-pyridin-3-yl-propionic acid (1B)



^{1}H NMR (CD_3OD): δ 8.55 (m, 1H), 8.43 (d, 1H), 7.85 (dt, 1H), 7.42 (dd, 1H), 5.08 (t, 1H), 2.87-2.74 (m, 1H), 1.40 (s, 9H).

HPLC-MS (Method B): m/z: 555 (2M+Na), 289 (M+Na), 267 (M+1); Rt = 0.80 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-3-oxo-1-pyridin-3-yl-propyl]-carbamic acid tert-butyl ester (1C)



^{1}H NMR (CD_3OD): δ 8.90 (s, 1H), 8.76 (m, 1H), 8.64 (m, 1H), 8.06 (m, 1H), 5.26 (t, 1H), 4.72-4.65 (m, 1H) 3.72-3.46 (m, 2H), 3.15-2.95 (m, 2H), 2.25-2.09 (m, 4H), 1.40 (s, 9H). HPLC-MS (Method B): m/z: 345 (M+1), 367 (M+23); Rt = 1.72 min.

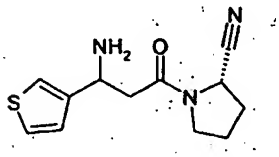
Step D: 1-(3-Amino-3-pyridin-3-yl-propionyl)-pyrrolidine-2-carbonitrile (1)

[3-(2-Cyano-pyrrolidin-1-yl)-3-oxo-1-pyridin-3-yl-propyl]-carbamic acid tert-butyl ester was reacted as described in general procedure (A), step D, to afford the title compound as an oil in 93 % yield.

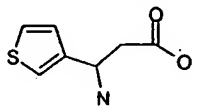
^{1}H NMR (CD_3OD): δ 8.95 (d, 1H), 8.8 (s, 1H), 8.48 (t, 1H), 7.9 (q, 1H), 5.05 (m, 1H), 4.74 (m, 1H), 3.65 (m, 1H), 3.5 (m, 1H), 3.26 (m, 2H), 2.22 (m, 2H), 2.14 (m, 2H). HPLC-MS (Method B): m/z:245 (M+1), 267 (M+Na); Rt = 0.29 min.

Example 2 (General procedure (A)

1-(3-Amino-3-thiophen-3-yl-propionyl)-pyrrolidine-2-(R)-carbonitrile (2)



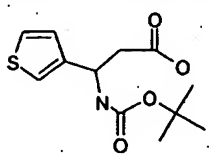
Step A: 3-Amino-3-thiophen-3-yl-propionic acid



^{1}H NMR (CD_3OD): δ 7.51 (m, 2H), 7.21 (dd, 1H), 4.64 (t, 1H), 2.72 (d, 2H)

HPLC-MS (Method B): m/z: 194 (M+Na), 172 (M+1), 155, 137, 113; Rt = 0.36 min.

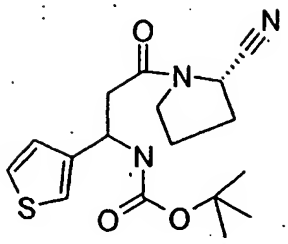
Step B: 3-tert-Butoxycarbonylamino-3-thiophen-3-yl-propionic acid (2B)



^{1}H NMR (CD_3OD): δ 7.35 (dd, 1H), 7.21 (m, 1H), 7.07 (dd, 1H), 5.13 (t, □1H), 2.76 (d, 2H), 1.42 (s, 9H).

HPLC-MS (Method B): m/z: 294 (M+Na), 238,155,137,113; Rt = 2.81 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-3-oxo-1-thiophen-3-yl-propyl]-carbamic acid tert-butyl ester (2C)



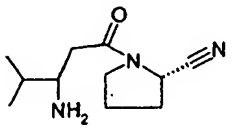
^{1}H NMR ($CDCl_3$): δ 7.29 (m, 1H), 7.18 (m 1H), 7.05 (dd, 1H), 6.09 (broad s, 1H), 5.18 (m, 1H), 4.66 (m, 1H), 3.40-3.25 (m, 2H), 2.93-2.86 (m, 1H), 2.78-2.73 (dd, 1H), 2.27-2.07 (m, 4H), 1.42 (s, 9H). HPLC-MS (Method B): m/z: 721(2M+Na), 372(M+Na), 250(M-Boc+1), 233; Rt = 3.36 min.

Step D: 1-(3-Amino-3-thiophen-3-yl-propionyl)-pyrrolidine-2-(R)-carbonitrile (2)

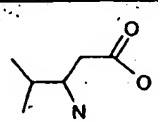
[3-(2-Cyano-pyrrolidin-1-yl)-3-oxo-1-thiophen-3-yl-propyl]-carbamic acid tert-butyl ester was reacted as described in general procedure (A), step D, to afford the title compound as an oil. ^{1}H NMR (CD_3OD): δ 7.59 (s, 1H), 7.54 (d, 1H), 7.25 (d, 1H), 4.89 (m, 1H), 4.77 (m, 1H), 3.63 (m, 1H), 3.49 (m, 1H), 3.09 (m, 2H), 2.24 (m, 2H), 2.13 (m, 2H). HPLC-MS (Method D): m/z: 272 (M+Na), 250 (M+1), 233, 191; Rt. = 0.47 min.

Example 3 (General procedure (A))

1-(3-Amino-4-methyl-pentanoyl)-pyrrolidine-2-carbonitrile (3)



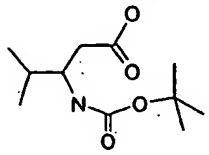
Step A: 3-Amino-4-methyl-pentanoic acid



^{1}H NMR (D_2O): δ 3.38-3.31 (m, 1H), 2.59 (dd, 1H), 2.41 (dd, 1H), 1.96 □(m, 1H), 1.46 (m, 6H).

HPLC-MS (Method B): m/z: 132 (M+1); Rt = 0.414 min.

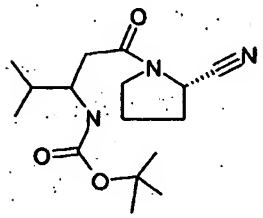
Step B: 3-tert-Butoxycarbonylamino-4-methyl-pentanoic acid (3B)



^{1}H NMR ($CDCl_3$): δ 5.81 (broad s, 1H), 4.96 (broad d, 1H), 3.75 (m, 1H), 2.54 (m, 1H), 1.84 (m, 1H), 1.45 (s, 9H).

HPLC-MS (Method B): m/z: 254 (M+Na), 232 (M+1), 132 (M-BOC+1); Rt = 2.48 min.

Step C: {1-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-2-methyl-propyl}-carbamic acid tert-butyl ester (3C)



^{1}H NMR ($CDCl_3$): δ 5.30 (m, 1H), 4.70 (m, 1H), 3.67 (m, 2H), 3.49 (m, 1H), 2.64-2.49 (m, 2H), 2.32-2.11 (m,4H), 1.43 (m, 9H), 0.94 (m, 6H). HPLC-MS (Method B): m/z : 332 (M+Na), 254, 210 (M-Boc+1); Rt = 2.85 min.

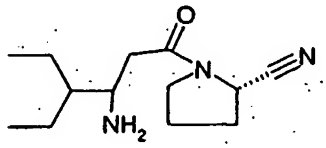
Step D: 1-(3-Amino-4-methyl-pentanoyl)-pyrrolidine-2-carbonitrile (3)

1-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-2-methyl-propyl}-carbamic acid tert-butyl ester was reacted as described in general procedure (A), step D, to afford the title compound as white crystals in 22 % yield.

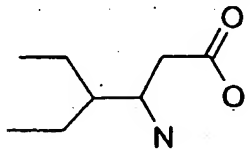
(CD_3OD): δ 4.79 (t, 1H), 3.68 (m, 1H), 3.48 (m, 2H), 2.83 (dt, 1H), 2.59 (m, 1H), 2.27 (m, 2H), 2.17 (m, 2H), 2.02 (m, 1H), 1.04 (m, 6H). HPLC-MS (Method D): m/z: 210 (M+1); Rt = 0.82 min.

Example 4 (General procedure (A))

1-(3-Amino-4-ethyl-hexanoyl)-pyrrolidine-2-carbonitrile (4)



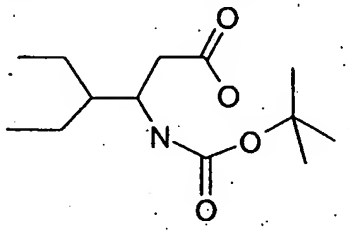
Step A: 3-Amino-4-ethyl-hexanoic acid



^{1}H NMR (D_2O): δ 3.60 (m 1H), 2.56 (dd, 1H), 2.42 (dd, 1H), 1.54-1.32 (m, 4H), 0.92 (dq, 6H).

HPLC-MS (Method B): m/z: 182 (M+Na), 160 (M+1), 143, 125, 110; Rt = 0.82 min.

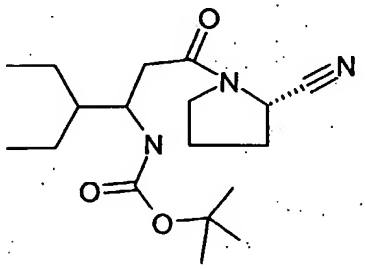
Step B: 3-tert-Butoxycarbonylamino-4-ethyl-hexanoic acid



^{1}H NMR ($CDCl_3$): δ 5.86 (broad s, 1H), 4.89 (broad d, 1H), 4.01 (m, 1H), 2,53 (m, 2H), 1.60 (m, 1H), 1.50-1.26 (m, 12H), 0.91 (m, 6H).

HPLC-MS (Method B): m/z: 542 (2M+Na), 282 (M+Na), 160(M-Boc+1); Rt = 3.17 min.

Step C: {1-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-2-ethyl-butyl}-carbamic acid tert-butyl ester



^{1}H NMR ($CDCl_3$): δ 5.26-5.17 (m, 1H), 4.72 (m, 1H), 3.93 (broad s, 1H), □3.66 (m, 1H), 3.50 (m, 1H), 2.53 (m, 2H), 2.31-2.11 (m, 4 H), 1.43 (m, 9H), 1.36-1.22 (m, 4H), 0.90 (t, 6H).

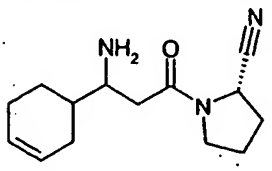
HPLC-MS (Method B): m/z: 360(M+Na), 282,2 60, 238(M-Boc+1); Rt = 3.51 min.

Step D: 1-(3-Amino-4-ethyl-hexanoyl)-pyrrolidine-2-carbonitrile (4)

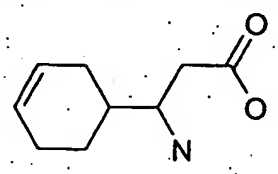
^{1}H-NMR (CD_3OD): δ 4.80 (m, 1H), 3.80-3.40 (m, 3H), 2.90-2.55 (m, 2H) 2.30-2.10 (m,4H), 1.55-1.30 (m,4H), 0.95 (m, 6H). HPLC-MS (Method D): m/z = 238 (M+1); Rt = 1.2 min.

Example 5 (General procedure (A))

1-(3-Amino-3-cyclohex-3-enyl-propionyl)-pyrrolidine-2-carbonitrile



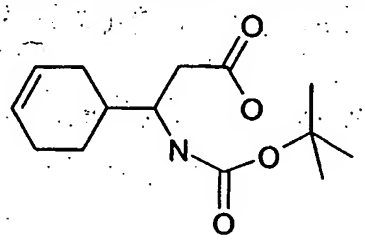
Step A: 3-Amino-3-cyclohex-3-enyl-propionic acid



^{1}H NMR (D_2O): δ 5.76 (m, 2H), 3.43 (m, 1H), 2.68-2.20 (m, 1H), 2.48-2.40 (m, 1H), 2.17–2.06 (m, 3H), 1.95-1.81(m, 3H), 1.35 (m, 1H)

HPLC-MS (Method B): m/z: 170 (M+1), 110; Rt = 0.73 min.

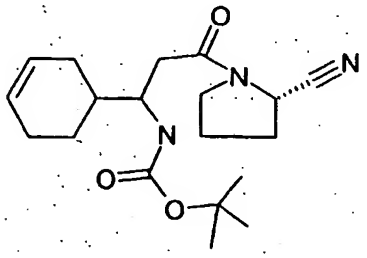
Step B: 3-tert-Butoxycarbonylamino-3-cyclohex-3-enyl-propionic acid



^{1}H NMR ($CDCl_3$): δ 5.67 (m, 2H), 4.97 (dd, 1H), 3.83 (broad d, 1H), 2.61 (m, 2H), 2.18–1.98 (m, 3H), 1.90-1.72 (m, 3H), 1.44 (s, 9H), 1.29 (m, 1H).

HPLC-MS (Method B): m/z: 561(2M+Na), 292(M+Na), 170(M-Boc+1); Rt = 3.02 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-1-cyclohex-3-enyl-3-oxo-propyl]-carbamic acid tert-butyl ester



^{1}H NMR ($CDCl_3$): δ 5.66 (s, 2H), 4.70 (m, 1H), 3.85-3.39 (m, 4H), 2.58 (m, 2H), 2.31-1.70 (m, 8H), 1.42 (s, 9H), 1.27 (m, 2H). HPLC-MS (Method B): m/z: 370 (M+Na), 349 (M+1),314,292, 248 (M-Boc+1); Rt = 3.367 min.

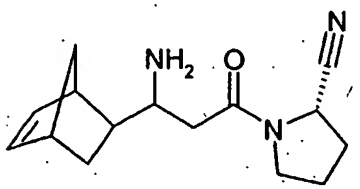
Step D: 1-(3-Amino-3-cyclohex-3-enyl-propionyl)-pyrrolidine-2-carbonitrile

^{1}H-NMR (CD_3OD): δ 5.72 (m, 2H), 4.79 (t, 1H), 3.69 (m, 1H), 3.55 (m, 2H), 2.88 (m, 1H), 2.65

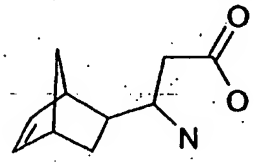
(m, 1H), 2.26 (m, 2H), 2.16 (m, 5H), 1.96 (m, 2H), 1.86 (m, 2H), 1.38 (m, 2H). HPLC-MS (Method D): m/z = 270 (M+Na), 248 (M+1); Rt = 1.16 min.

Example 6 (General procedure (A))

1-(3-Amino-3-bicyclo[2.2.1]hept-5-en-2-yl-propionyl)-pyrrolidine-2-carbonitrile



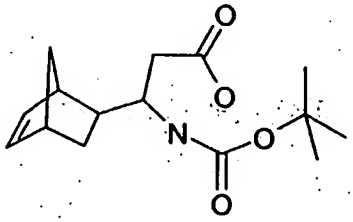
Step A: 3-Amino-3-bicyclo[2.2.1]hept-5-en-2-yl-propionic acid



^{1}H NMR (D_2O): δ 6.34 (m, 1H), 6.19 (m, 1H), 6.06 (m, 1H), 3.32 (m), 2.99 (broad s,), 2.93-2.80 (m, 3H), 2.77-2.63 (m), 2.55 (dd, 1H), 2.51-2.44(m), 2.35 (dd, 1H), 2.27 (m, 1H), 1.96 (m, 1H), 1.56 (m), 1.49 (m, 1H), 1.44-1.27 (m), 0.84 (m), 0.68 (m, 1H)

HPLC-MS (Method B): m/z: 204 (M+Na), 182(M+1); Rt = 0.84 min.

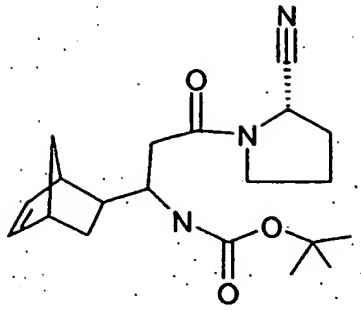
Step B: 3-Bicyclo[2.2.1]hept-5-en-2-yl-3-tert-butoxycarbonylamino-propionic acid



^{1}H NMR ($CDCl_3$): δ 6.19 (m, 1H), 6.08 (,m,1H), 6.01 (broad m, 1H), 5.08 (m, 1), 3.26 (broad s, 1H), 2.84 (m, 2H), 2.77-2.41 (m), 2.29 (m, 1H), 1.82 (m, 1H), 1.45 (s, 9H), 1.25 (m, 2H), 0.84 (m), 0.58 (m).

HPLC-MS (Method B): m/z: 586 (2M+Na), 304 (M+Na), 182(M-Boc+1); Rt = 3.14 min.

Step C: [1-Bicyclo[2.2.1]hept-5-en-2-yl-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl



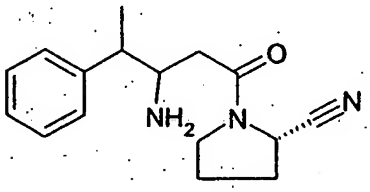
^{1}H NMR ($CDCl_3$): δ 6.16-6.02 (m, 1H), 5.48 (m, 1H), 4.72 (m, 1H), 4.40 (broad s, 1H), 3.68-3.20 (m, 3H), 2.90-2.47 (m,5 H) , 2.31-2.07 (m, 4H), 1.79 (m, 1H), 1.43 (m, 10H), 1.24 (m,1H). HPLC-MS (Method B): m/z: 382 (M+Na), 333, 304, 282, 260(M-Boc+1); Rt = 3.48 min.

Step D: 1-(3-Amino-3-bicyclo[2.2.1]hept-5-en-2-yl-propionyl)-pyrrolidine-2-carbonitrile

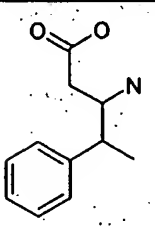
^{1}H-NMR (CD_3OD): δ 6.32 (m), 6.15 (m), 6.10 (m), 5.69 (m), 4.77 (m, 1H), 3.65 (m, 1½H), 3.48 (m, 1½H), 3.1 - 2.8 (m, 3H), 2.78 (m, 1H), 2.62 (m, 1H), 2.34 (m, 1H), 2.25 (m, 2H), 2.16 (m, 2H), 1.96 (m, 1H), 1.6 - 1.35 (m, 2H). HPLC-MS (Method D): m/z = 282 (M+Na), 260 (M+1); Rt = 1.25 min.

Example 7 (General procedure (A)

1-(3-Amino-4-phenyl-pentanoyl)-pyrrolidine-2-carbonitrile



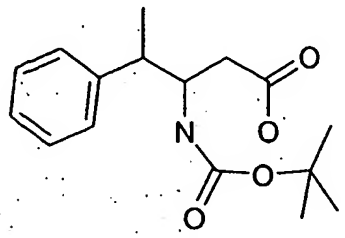
Step A: 3-Amino-4-phenyl-pentanoic acid



^{1}H NMR (D_2O): δ 7.48-7.32 (m, 5H), 3.86 (m, 1H), 3.15-3.00 (m, 1H), 2.8-2.7 (m), 2.54-2.40 (m, 1H) 2.28-2.22 (m), 1.4-1.34 (dd, 3H).

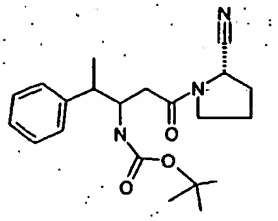
HPLC-MS (Method B): m/z: 194 (M+1); Rt = 0.68 min.

Step B: 3-tert-Butoxycarbonylamino-4-phenyl-pentanoic acid



HPLC-MS (Method B): m/z: 610 (2M+Na), 316 (M+Na), 194(M-Boc+1); Rt = 3.18 min.

Step C: {1-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-2-phenyl-propyl}-carbamic acid tert-butyl ester



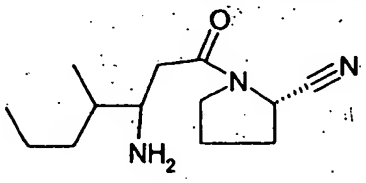
^{1}H NMR ($CDCl_3$): δ 7.31 (m, 2H), 7.25-7.13 (m, 3H), 4.69 (m, 1H), 4.22(broad s, 1H), 3.58-3.20 (M, 2H), 3.03 (m, 1H), 2.67-2.42 (m, 2H), 2.32-1.92 (m, 4H), 1.50-1.25 (m, 12H). HPLC-MS (Method B): m/z: 394(M+Na), 372(M+1), 291,272(M-Boc+1); Rt = 3.819 min.

Step D: 1-(3-Amino-4-phenyl-pentanoyl)-pyrrolidine-2-carbonitrile

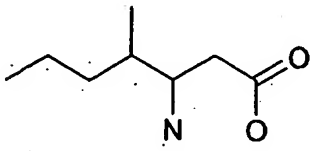
^{1}H-NMR (CD_3OD): δ 7.43 - 7.22 (m, 5H), 4.75 (m), 4.66 (m), 3.87 - 3.71 (m, 1H) 3.66 (m), 3.47 (m) 3.34 (m), 3.2 (m) 3.05 - 2.79 (m), 2.70 - 2.52 (m), 2.42 (t), 2.34 (t), 2.25 (m, 1H), 2.16 (m, 2H), 2.02 (m, 1H), 1.43 (d), 1.38 (d). HPLC-MS (Method D): m/z = 272 (M+1); Rt = 1.35 min.

Example 8 (General procedure (A))

1-(3-Amino-4-methyl-heptanoyl)-pyrrolidine-2-carbonitrile



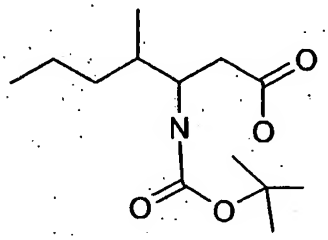
Step A: 3-Amino-4-methyl-heptanoic acid



^{1}H NMR (D_2O + DMSO-d_6): δ 3.43 (m, 1H), 2.56-2.48 (m, 1H), 2.44-2.33(m, 1H), 1.79 (broad s, 1H), 1.38 (m, 2H), 1.31-1.14 (m, 2H), 0.90-0.86 (dt, 6H).

HPLC-MS (Method B): m/z : 182 (M+Na), 160 (M+1), 143, 125, 100; Rt = 0.45 min.

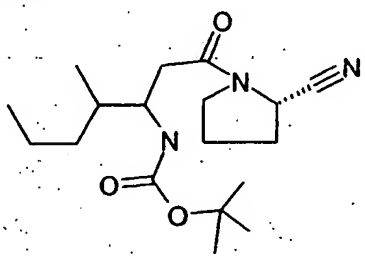
Step B: 3-tert-Butoxycarbonylamino-4-methyl-heptanoic acid



^{1}H NMR ($CDCl_3$): δ 3.86 (m, 2H), 2.50 (m, 1H), 1.70 (m, 1H), 1.44-1.46 (m), 1.20-1.14 (m).

HPLC-MS (Method B): m/z : 282 (M+Na), 226,204,186,160 (M-Boc+1), 144, 125, 100; Rt = 3.53 min.

Step C: {1-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-2-methyl-pentyl}-carbamic acid tert-butyl ester



^{1}H NMR ($CDCl_3$): δ 4.86-4.65 (m, 1H), 3.92-4.41 (m, 3H), 2.54 (m, 2H), 2.38-2.05 (m, 4H), 1.41 (m, 9H), 1.34 (m, 3H), 1.06 (m, 2H), 0.89 (dd, 6H). HPLC-MS (Method B): m/z: 360 (M+Na), 338 (M+1), 238(M-Boc+1); Rt = 3.86 min.

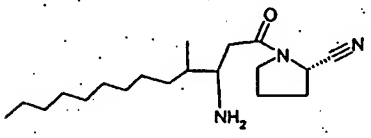
Step D: 1-(3-Amino-4-methyl-heptanoyl)-pyrrolidine-2-carbonitrile

^{1}H-NMR (CD_3OD): δ 4.79 (t, 1H), 3.76-3.44 (m, 4H), 2.86-2.55 (m, 2H), 2.28-2.12 (m, 4H), 1.52-1.18 (m, 4H), 1.05-0.90 (m, 8H). HPLC-MS (Method D): m/z = 238 (M+1); Rt = 1.26

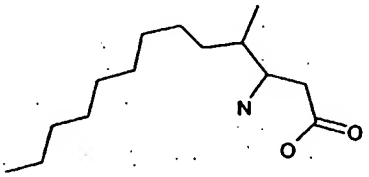
min.

Example 9 (General procedure (A)

1-(3-Amino-4-methyl-tridecanoyl)-pyrrolidine-2-carbonitrile

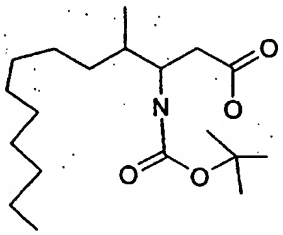


Step A: 3-Amino-4-methyl-tridecanoic acid



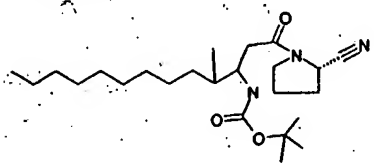
HPLC-MS (Method B): m/z: 266(M+Na), 244(M+1); Rt = 3.01 min.

Step B: 3-tert-Butoxycarbonylamino-4-methyl-tridecanoic acid



HPLC-MS (Method B): m/z: 709 (2M+Na), 366 (M+Na), 288, 270, 244 (M-Boc+1); Rt = 5.52 min.

Step C: {1-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-2-methyl-undecyl}-carbamic acid tert-butyl ester



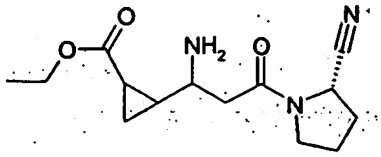
^{1}H NMR ($CDCl_3$): δ 4.70 (m, 1), 3.79-3.44 (m, 2H), 2.52 (m, 2H), 2.35-2.07 (m, 4H), 1,75 (broad m, 1H), 1.42 (m, 9H), 1.25 (s, 16 H), 0.88 (t, 6H). HPLC-MS (Method B): m/z: 865/866 (2M+Na), 444 (M+Na), 366(M-Boc+Na), 322 (M-Boc+1); Rt = 5.75 min.

Step D: 1-(3-Amino-4-methyl-tridecanoyl)-pyrrolidine-2-carbonitrile

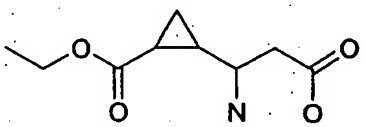
^{1}H-NMR (CD_3OD): δ 4.79 (t, 1H), 3.74-3.48 (m, 4H), 2.86-2.53 (m, 3H), 2.28-2.14 (m, 4H), 1.49-1.22 (m, 12H), 1.03-0.97 (m, 4H), 0.90 (t, 6H). HPLC-MS (Method D): m/z = 643 (2M+1), 322 (M+1), 184; Rt = 3.30 min.

Example 10 (General procedure (A)

2-[1-Amino-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-cyclopropanecarboxylic acid ethyl ester



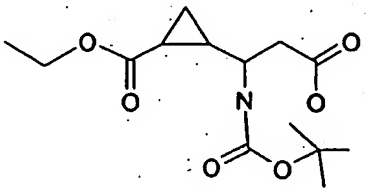
Step A: 2-(1-Amino-2-carboxy-ethyl)-cyclopropanecarboxylic acid ethyl ester



^{1}H NMR (D_2O): δ 4.17 (q, 2H), 2.96 (m, 1H), 2.69-2.56 (m, 2H), 1.93-1.82 (m, 1H), 1.69 (m, 1H), 1.33 (m, 1H), 1.26 (t, 3H), 1.17 (m, 1H).

HPLC-MS (Method B): m/z:224 (M+Na), 202 (M+1), 185, 139; Rt = 0.41 min.

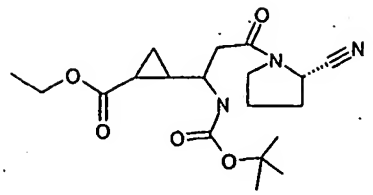
Step B: 2-(1-tert-Butoxycarbonylamino-2-carboxy-ethyl)-cyclopropanecarboxylic acid ethyl ester



^{1}H NMR ($CDCl_3$): δ 5.98 (broad s, 1H), 5.21 (broad s, 1H), 4.12 (q, 2H), 3.49 (m, 1H), 2.68 (broad s, 2H), 1.69 (m, 1H), 1.58 (m, 1H), 1.45 (s, 9H), 1.25 (t, 3H), 1.18 (m, 1H), 1.05 (m, 1H).

HPLC-MS (Method B): m/z: 324 (M+Na), 268, 202 (M-Boc+1), 185, 167,157,139; Rt = 2.88 min.

Step C: 2-[1-tert-Butoxycarbonylamino-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-cyclopropanecarboxylic acid ethyl ester



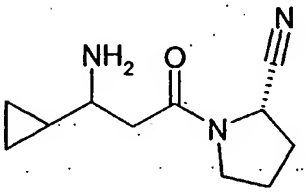
^{1}H NMR ($CDCl_3$): δ 5.74 (m, 1H), 4.73 (t, 1H), 4.10 (m, 2H), 3.66 (m, 1H), 3.49 (m, 2H), 2.72 (m, 1H), 2.63 (m, 1H), 2.35-2.09 (m, 3H), 1.77 (m, 1H), 1.54 (m, 1H), 1.43 (s, 9H), 1.24 (t, 3H), 1.15 (m, 1H). HPLC-MS (Method B): m/z: 402 (M+Na); 280(M-Boc+1); Rt = 3.25min.

Step D: 2-[1-Amino-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-cyclopropanecarboxylic acid ethyl ester

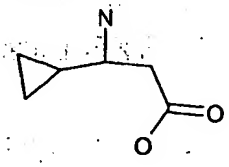
^{1}H NMR (CD_3OD): δ 4.78 (m, 1H), 4.12 (m, 2H), 3.75-3.45 (m, 2H), 3.14-2.78 (m, 4H), 2.29-2.13 (m, 4H), 1.85-1.65 (m, 2H), 1.17-1.03 (m, 1H). HPLC-MS (Method D): m/z: 559 (2M+1), 302 (M+Na), 280(M+1); Rt = 1.03 min.

Example 11 (General procedure (A)

1-(3-Amino-3-cyclopropyl-propionyl)-pyrrolidine-2-carbonitrile

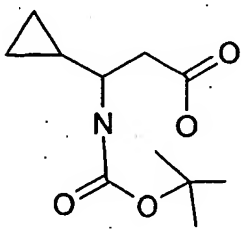


Step A: 3-Amino-3-cyclopropyl-propionic acid



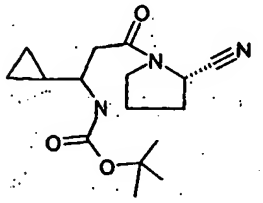
^{1}H NMR (D_2O+DMSO-d6): δ 2.76-2.66 (m, 1H), 2.69 (m, 1H), 2.22 (m, 1H), 1.23-1.19 (m, 1H), 1.01 (m, 1H), 0.86 (m, 1H), 0.66 (m, 1H), 0.40 (m, 1H).

Step B: 3-tert-Butoxycarbonylamino-3-cyclopropyl-propionic acid



HPLC-MS (Method B): m/z: 252 (M+Na), 196, 174, 156, 130 (M-Boc+1), 113; Rt = 2.47 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-1-cyclopropyl-3-oxo-propyl]-carbamic acid tert-butyl ester



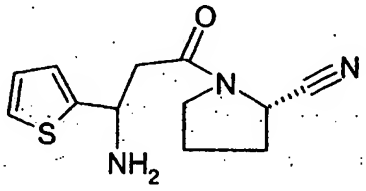
^{1}H NMR ($CDCl_3$): δ 4.46 (m, 1H), 3.51 (m, 2H), 3.36 (m, 2H), 2.35-1.93 (m, 8H), 1.51 (m, 12H). HPLC-MS (Method B): m/z: 330 (M+Na), 208 (M-Boc+1), 191; Rt = 2.98 min.

Step D: 1-(3-Amino-3-cyclopropyl-propionyl)-pyrrolidine-2-carbonitrile

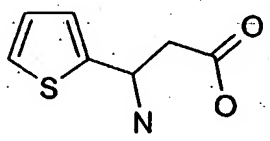
HPLC-MS (Method D): m/z: 230 (M+Na), 208 (M+1), 191; Rt = 0.73 min.

Example 12 (General procedure (A)

1-(3-Amino-3-thiophen-2-yl-propionyl)-pyrrolidine-2-carbonitrile



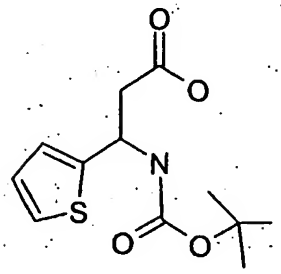
Step A: 3-Amino-3-thiophen-2-yl-propionic acid



^{1}H NMR (D_2O+CD_3OD): δ 7.50 (dd, 1H), 7.26 (dd, 1H), 7.06 (dd, 1H), 4.88 (dd, 1H), 2.85 (m, 2H).

HPLC-MS (Method B): m/z:155 (M-NH3), 137, 113; Rt = 3.15 min

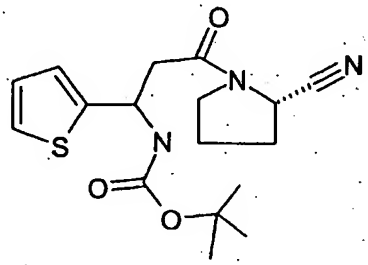
Step B: 3-tert-Butoxycarbonylamino-3-thiophen-2-yl-propionic acid



^{1}H NMR ($CDCl_3$): δ 7.20 (m, 1H), 6.94 (m, 2H), 5.48 (broad s, 1H), 5.36 (broad s, 1H), 2.95 (m, 2H), 1.45 (s, 9H).

HPLC-MS (Method B): m/z: 294 (M+Na), 155, 137, 113; Rt = 2.95 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-3-oxo-1-thiophen-2-yl-propyl]-carbamic acid tert-butyl ester



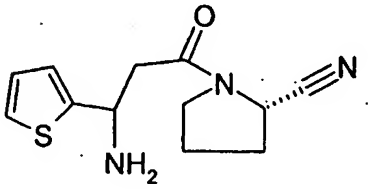
^{1}H NMR ($CDCl_3$): δ 7.16 (m, 1H), 6.92 (m, 2H), 5.37 (m, 1H), 4.67 (m, 1H), 3.56 (m, 1H), 3.29 (m, 1H), 2.97 (dd, 1H), 2.85 (dd, 1H), 2.30-2.04 (m, 5H), 1.44 (s, 9H). HPLC-MS (Method B): m/z: 721 (2M+Na), 372 (M+Na), 250(M-Boc+1), 233; Rt = 3.36 min.

Step D: 1-(3-Amino-3-thiophen-2-yl-propionyl)-pyrrolidine-2-carbonitrile

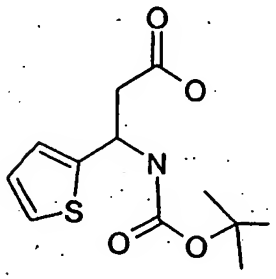
(CD_3OD): δ 7.53 (d, 1H), 7.31 (d, 1H), 7.10 (dd, 1H), 5.1 (m, 1H), 4.81 (m, 1H), 3.71-3.65 (m, 1H), 3.17 (t, 2H), 2.30-2.10 (m, 4H) HPLC-MS (Method D): m/z: 272 (M+Na), 250 (M+1), 233, 191, 123; Rt = 0.87 min.

Example 13 (General procedure (A)

1-(3-Amino-3-thiophen-2-yl-propionyl)-pyrrolidine-2-carbonitrile



Step B: 3-tert-Butoxycarbonylamino-3-thiophen-2-yl-propionic acid

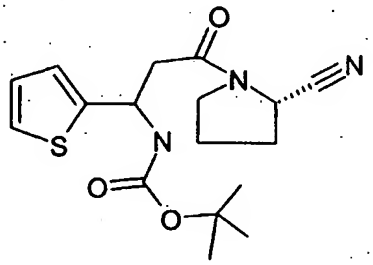


NB! Stoffet adskilt i to isomerer vha HPLC

^{1}H NMR ($CDCl_3$): δ 7.20 (m, 1H), 6.94 (m, 2H), 5.48 (broad s, 1H), 5.36 (broad s, 1H), 2.95 (m, 2H), 1.45 (s, 9H).

HPLC-MS (Method B): m/z: 294 (M+Na), 155, 137, 113; Rt = 2.95 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-3-oxo-1-thiophen-2-yl-propyl]-carbamic acid tert-butyl ester



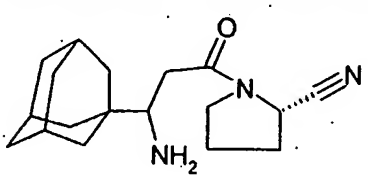
^{1}H NMR ($CDCl_3$): δ 7.20 (m, 1H), 6.95 (m, 2H), 6.13 (d, 1H), 5.36 (m, 1H), 4.67 (m, 1H), 3.47 (m, 1H), 3.39 (m, 1H), 2.98 (dd, 1H), 2.84 (dd, 1H), 2.27-2.04 (m, 4H), 1.43 (s, 9H). HPLC-MS (Method B): m/z: 721(2M+Na), 372 (M+Na), 250(M-Boc+1), 233; Rt = 3.038 min.

Step D: 1-(3-Amino-3-thiophen-2-yl-propionyl)-pyrrolidine-2-carbonitrile

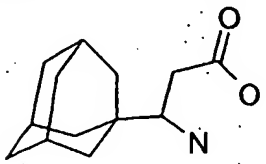
(CD_3OD): δ 7.52 (d, 1H), 7.28 (d, 1H), 7.09(dd, 1H), 5.07 (t, 1H) 4.78 (t, 1H), 3.67 (m, 1H), 3.50 (m, 1H), 3.15 (d, 2H)), 2.3-2.1 (m, 4H). HPLC-MS (Method D): m/z: 272(M+Na), 250 (M+1), 233; Rt = 0.55 min.

Example 14 (General procedure (A)

1-(3-Adamantan-1-yl-3-amino-propionyl)-pyrrolidine-2-carbonitrile

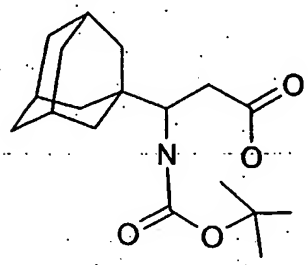


Step A: 3-Adamantan-1-yl-3-amino-propionic acid



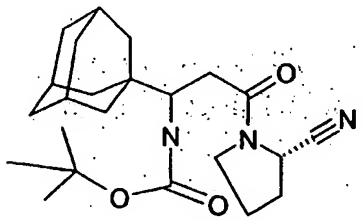
^{1}H NMR (DMSO-d6+CD_3OD): δ 2.77 (m, 1H), 2.20 (m, 1H), 1.98 (m, 4H), 1.70-1.48 (m, 12H)
HPLC-MS (Method B): m/z: 469 (2M+Na), 224(M+1), 207, 166; Rt = 1.76 min.

Step B: 3-Adamantan-1-yl-3-tert-butoxycarbonylamino-propionic acid



^{1}H NMR ($CDCl_3$): δ 4.75 (broad d, 1H9, 3.80-3.61 (m, 2H), 2.33-2.22 (m, 1H), 1.79-1.47 (m, 15 H), 1.44 (s, 9H)
HPLC-MS (Method B): m/z: 346 (M+Na), 268, 250, 224 (M-Boc-1); Rt = 3.83 min.

Step C: [1-Adamantan-1-yl-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester



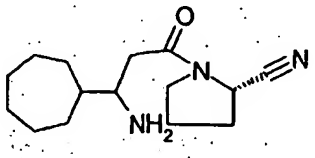
^{1}H NMR ($CDCl_3$): δ 5.00 (dd, 1H), 4.67 (dd, 1H), 3.81-3.60 (m, 3H), 3.48 (m, 1H), 2.60 (dt, 1H), 2.33-2.09 (m, 4H), 1.77-1.47 (m, 16H), 1.41 (m, 9H). HPLC-MS (Method B): m/z: 825(2M+Na), 424(M+Na), 302(M-Boc+1); Rt = 4.40 min.

Step D: 1-(3-Adamantan-1-yl-3-amino-propionyl)-pyrrolidine-2-carbonitrile

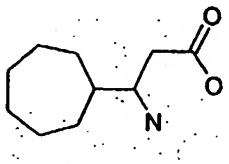
(DMSO-d_6): δ 4.80-4.73 (m, 1H), 3.75-3.39 (m, 3H), 2.85-2.74 (m, 1H), 2.46-2.35 (m, 1H), 2.16 (m, 2H), 2.08-1.97 (m), 1.69-1.54 (m) (1A)
HPLC-MS (Method B): m/z: 324 (M+Na), 302 (M+1); Rt = 1.91 min.

Example 15 (General procedure (A)

1-(3-Amino-3-cycloheptylpropionyl)-pyrrolidine-2-carbonitrile



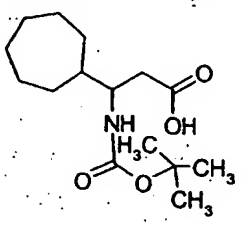
Step A: 3-Amino-3-cycloheptylpropionic acid



^{1}H NMR (D_2O): δ 3.45 (m, 1H), 2.53 (d.d., 1H), 2.42 (d.d., 1H), 1.90-1.25 (m, 12H)

HPLC-MS (Method B): m/z: 186 (M+1); Rt = 1.19 min.

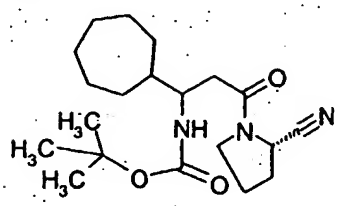
Step B: 3-tert-Butoxycarbonylamino-3-cycloheptyl-propionic acid



^{1}H NMR ($CDCl_3$): δ 4.90 (m, 2H), 3.84 (m, 1H), 2.52 (m, 2H), 1.70 (m, 4H), 1.61-1.41 (m, 14H), 1.26 (m, 2H)

HPLC-MS (Method B): m/z: 308 (M+Na), 286 (M+1), 212, 186 (M-Boc+1), Rt = 3.848 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-1-cycloheptyl-3-oxo-propyl]-carbamic acid tert-butyl ester



^{1}H NMR ($CDCl_3$): δ 5.26-5.15 (m), 4.71 (m, 1H), 4.43 (broad s), 3.77 (m, 1H), 3.64 (m, 1H), 3.50 (m, 1H), 2.52 (m, 2H), 2.33-2.11 (m, 4H), 1.85-1.52 (m, 9H), 1.43 (m, 9-11H), 1.26 (m, 2-3H).

HPLC-MS (Method B): m/z: 386 (M+Na), 264 (M-BOC+1); Rt = 4.152 min.

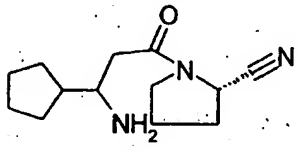
Step D: 1-(3-Amino-3-cycloheptyl-propionyl)-pyrrolidine-2-carbonitrile.

^{1}H NMR (D2O): δ 3.45 (m, 1H), 2.53 (d.d., 1H), 2.42 (d.d., 1H), 1.90-1.25 (m, 12H).

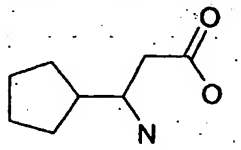
HPLC-MS (Method B): m/z: 549 (2M+Na), 264 (M+1), Rt = 1.816 min og 1.936 min.

Example 16 (General procedure (A)

1-(3-Amino-3-cyclopentylpropionyl)-pyrrolidine-2-carbonitrile

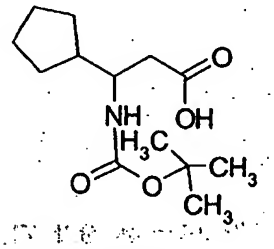


Step A: 3-Amino-3-cyclopentylpropionic acid



HPLC-MS (Method B): m/z: 158 (M+1); Rt = 0.47 min.

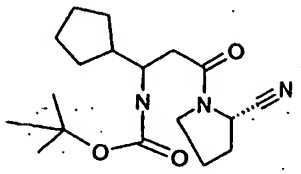
Step B: 3-tert-Butoxycarbonylamino-3-cyclopentylpropionic acid



^{1}H NMR ($CDCl_3$): δ 5.0 (broad d, 1H), 3.76 (broad s, 1H), 2.67-2.45 (m, 2H), 1.82-1.51 (m, 7H), 1.44 (s, 9H), 1.34-1.15 (m, 2H).

HPLC-MS (Method B): m/z: 280 (M+Na), 258 (M+1), 184, 158 (M-Boc+1), 142, 123 ; rt = 3.282 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-1-cyclopentyl-3-oxo-propyl]-carbamic acid tert-butyl ester

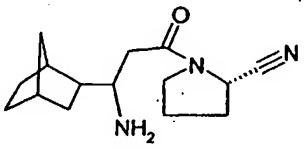


^{1}H NMR ($CDCl_3$): δ 5.47-5.35 (broad m, 1H), 4.73 (m, 1H), 3.77-3.56 (m, 1H), 2.34-2.09 (m, 5-6H), 1.86-1.49 (m, 9-10 H), 1.42-1.43 (d, 9H), 1.29 (m, 1H), 1.15 (m, 1H).
HPLC-MS (Method B): m/z: 358 (M+Na), 236 (M-BOC+1); Rt = 3.63 min.

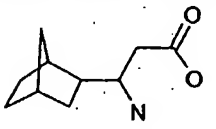
Step D: **1-(3-Amino-3-cyclopentyl-propionyl)-pyrrolidine-2-carbonitrile**

^{1}H NMR (CD_3OD): δ 4.78 (t, 1H), 3.73-3.64 (m, 1H), 3.56-3.39 (m, 2H), 2.91-2.82 (dt, 1H), 2.66-2.56 (m, 1H), 2.29-2.07 (m, 5H), 1.90 (m, 1H), 1.79-1.62 (m, 4H), 1.32 (m, 2H).
HPLC-MS (Method B): m/z: 258 (M+Na), 236 (M+1); Rt = 1.02 min and 1.31 min.

Example 17 (General procedure (A) **1-(3-Amino-3-bicyclo[2.2.1]hept-2-yl-propionyl)-pyrrolidine-2-carbonitrile**

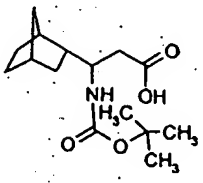


Step A: 3-Amino-3-bicyclo[2.2.1]hept-2-yl-propionic acid



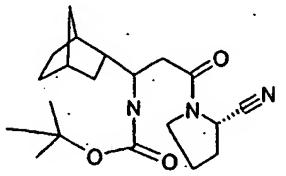
HPLC-MS (Method B): m/z: 184 (M+1); Rt = 0.79 min.

Step B: 3-Bicyclo[2.2.1]hept-2-yl-3-tert-butoxycarbonylamino-propionic acid.



^{1}H NMR ($CDCl_3$): δ 5.08 (broad d), 4.88 (broad d), 3.55 (broad s, 1H), 2.71-2.38 (m, 2H), 2.23 (m, 2H), 1.60-1.48 (m, 3H), 1.45 (s, 9H), 1.39-1.22 (m, 3H), 1.14 (m, 3H).
HPLC-MS (Method B): m/z: 306 (M+Na), 184 (M-BOC+1); Rt = 3.65 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-1-cyclopentyl-3-oxo-propyl]-carbamic acid tert-butyl ester



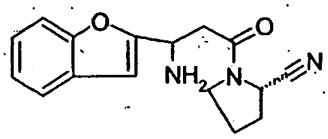
HPLC-MS (Method B): m/z: 384 (M+Na), 262 (M-BOC+1); Rt = 3.98 min.

Step D: **1-(3-Amino-3-bicyclo[2.2.1]hept-2-yl-propionyl)-pyrrolidine-2-carbonitrile**

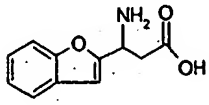
^{1}H NMR (CD_3OD): δ 4.78 (m, 1H), 3.67 (m, 1H), 3.51 (m, 1H), 3.26 (m, 1H), 3.01-2.93 (m, 1H), 2.88-2.47 (m, 2H), 2.38-2.01 (m, 6H), 1.77-1.15 (m, 8H).

HPLC-MS (Method B): m/z: 523 (2M+1), 262 (M+1); Rt = 1.47 min and 1.69 min.

Example 18 (General procedure (A) **1-(3-Amino-3-benzofuran-2-yl-propionyl)-pyrrolidine-2-carbonitrile**

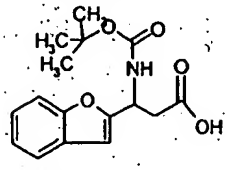


Step A: 3-Amino-3-benzofuran-2-yl-propionic acid



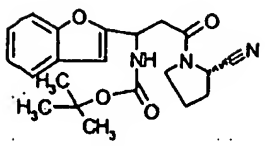
HPLC-MS (Method B): m/z: 228 (M+Na), 206 (M+1), 189 (M-NH3+1); Rt = 0.92 min.

Step B: 3-Benzofuran-2-yl-3-tert-butoxycarbonylamino-propionic acid.



HPLC-MS (Method B): m/z: 328 (M+Na), 272, 189, 147; Rt = 3.44 min.

Step C: [1-Benzofuran-2-yl-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester.



HPLC-MS (Method B): m/z: 789 (2M+Na), 406 (M+Na), 284 (M-Boc+1), 267; Rt = 1.69 min.

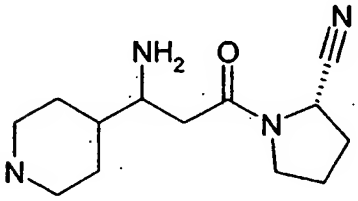
Step D: **1-(3-Amino-3-benzofuran-2-yl-propionyl)-pyrrolidine-2-carbonitrile**

^{1}H NMR (CD_3OD): δ 7.65 (d, 1H), 7.55 (d, 1H), 7.35 (dd, 1H), 7.25 (dd, 1H), 5.05 (m, 1H), 4.78 (m, 1H), 3.68 (m, 1H), 3.53 (m, 1H), 3.22 (m, 2H), 2.22 (m, 2H), 2.15 (m, 2H)

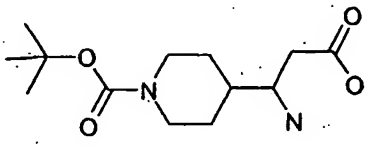
HPLC-MS (Method B): m/z: 322, 306 (M+Na), 284 (M+1), 267 ($M-NH_3$+1), 225, 173, 131, 123; Rt = 1.45 min.

Example 19 (General procedure (A)

1-(3-Amino-3-piperidin-4-yl-propionyl)-pyrrolidine-2-carbonitrile



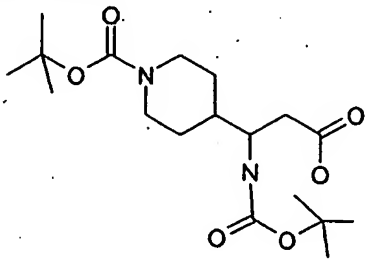
Step A: 4-(1-Amino-2-carboxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester



^{1}H NMR (D_2O): δ 4.14 (d, 2H), 3.39 (m, 1H), 2.80 (t, 2H), 2.61 (dd, 1H), 2.43 (dd, 1H), 1.88 (m, 1H), 1.77 (t, 2H), 1.45 (s, 9H), 1.31-1.22 (m, 2H) .

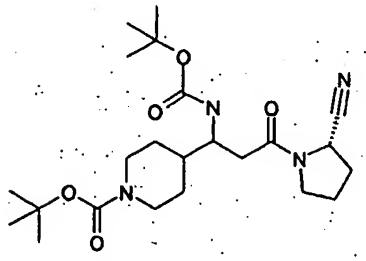
HPLC-MS (Method B): m/z: 295 (M+Na), 273 (M+1), 217; Rt = 1.30 min.

Step B: 4-(1-tertl-Butoxycarbonylamino-2-carboxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester



^{1}H NMR (CDCl3): δ 5.86 (broad s, 1H), 5.05 (broad s, 1H), 4.13 (m, 2H), □3.78 (broad s, 1H), 2.70-2.50 (m, 4H), 1.77-1.59 (m, 4H), 1.45 □(s, 9H), 1.19 (m, 2H).
HPLC-MS (Method B): m/z: 395 (M+Na), 273 (M-Boc+1), 217; Rt = 3.15 min.

Step C: 4-[1-tert-Butoxycarbonylamino-3-(2-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-piperidine-1-carboxylic acid tert-butyl ester



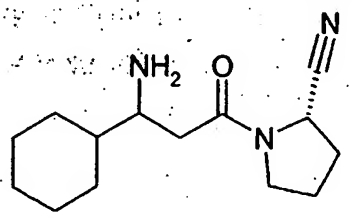
^{1}H NMR ($CDCl_3$): δ 5.44 (m, 1H), 4.71 (m, 1H), 4.13 (broad s, 1H), 3.68 (m, 2H), 3.48 (m, 1H), 2.74-2.51 (m, 4H), 2.33-2.09 (m, 4H), 1.81 (m, 2H), 1.57 (m, 1H), 1.45 (m, 9H), 1.15 (m, 2H). HPLC-MS (Method B): m/z: 473 (2M+Na), 351(M-Boc+1) 295, 251(M- 2 Boc+1); Rt = 3.38 min.

Step D: 1-(3-Amino-3-piperidin-4-yl-propionyl)-pyrrolidine-2-carbonitrile

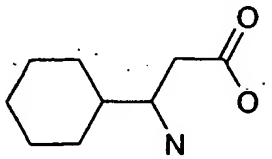
(DMSO-d_6): δ 4.80-4.74 (m, 1H), 3.69-3.57 (m, 1H), 3.50-3.30 (m, 4H), 2.90-2.70 (m, 3H), 2.55-2.52 (m, 1H), 2.20-1.77 (m, 8H), 1.49-1.37 (m, 2H). HPLC-MS (Method D): m/z: 273 (M+Na), 251 (M+1); Rt = 0.33 min.

Example 20 (General procedure (A))

1-(3-Amino-3-cyclohexyl-propionyl)-pyrrolidine-2-(S)-carbonitrile



Step A: 3-Amino-3-cyclohexyl-propionic acid

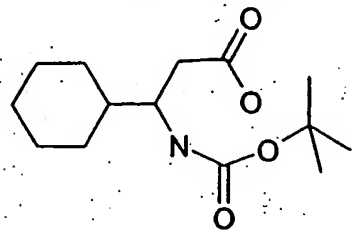


^{1}H NMR (D_2O): δ 3.38-3.31 (m, 1H), 2.60 (dd, 1H), 2.41 (dd, 1H), □1.81-1.57 (m, 6H), 1.33-

1.02 (m, 5H).

HPLC-MS (Method B): m/z: 194 (M+Na), 172 (M+1), 155, 137, 110; Rt = 0.87 min.

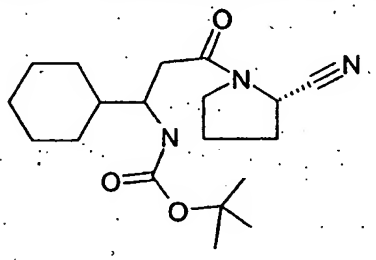
Step B: 3-tert-Butoxycarbonylamino-3-cyclohexyl-propionic acid



^{1}H NMR ($CDCl_3$): δ 5.72 (broad s, 1H), 4.96 (broad d, 1H), 3.74 (m, 1H), □2.57 (m, 2H), 1.86-1.59 (m, 5H), 1.44 (s, 10H), 1.28-1.09 (m, □3H), 1.07-0.91 (m, 2H).

HPLC-MS (Method B): m/z: 294 (M+Na), 273 (M+1), 172 (M-Boc+1); Rt = 3.255 min.

Step C: [3-(2-Cyano-pyrrolidin-1-yl)-1-cyclohexyl-3-oxo-propyl]-carbamic acid tert-butyl ester



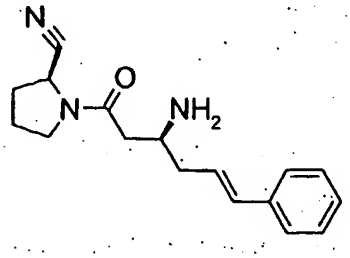
^{1}H NMR ($CDCl_3$): δ 5.34 (dd, 1H), 4.71 (m, 1H), 3.65 (m, 1H), 3.51 (m, 1H), 2.69-2.49 (m, 2H), 2.31-2.11(m, 3H), 1.90-1.53 (m, 5H), 1.43 (d, 9H), 1.20 (m, 3H), 0.95 (m, 2H). HPLC-MS (Method B): m/z: 372 (M+Na), 294,272,250 (M-Boc+1); Rt = 3.59 min.

Step D: 1-(3-Amino-3-cyclohexyl-propionyl)-pyrrolidine-2-(S)-carbonitrile

(CD_3OD): δ 4.78 (t, 1H), 3.74-3.62 (m, 1H), 3.57-3.40 m, 2H), □2.89-2.76 (m, 1H), 2.65-2.56 (m, 1H), 2.28-2.15 (m, 4H), 1.88-1.65 (m, 6H), 1.38-1.07 (m, 5H). HPLC-MS (Method D): m/z: 272 (M+Na), 250 (M+1); Rt = 1.27 min.

Example 21 (General procedure (B))

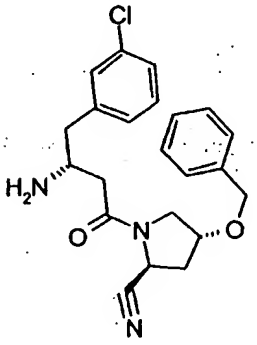
1-(3-Amino-6-phenyl-hex-5-enoyl)-pyrrolidine-2-carbonitrile



HPLC-MS (Method B): *m/z* = 284 (M+1); R_t = 2.9 min.

Example 22 (General procedure (B))

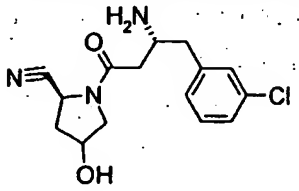
1-[3-Amino-4-(3-chloro-phenyl)-butyryl]-4-benzyloxy-pyrrolidine-2-carbonitrile



HPLC-MS (Method B): *m/z* = 397 (M+1); R_t = 3.5 min.

Example 23 (General procedure (B))

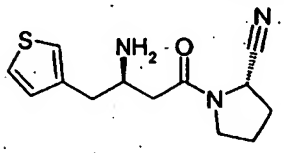
1-[3-Amino-4-(3-chloro-phenyl)-butyryl]-4-hydroxy-pyrrolidine-2-carbonitrile



HPLC-MS (Method B): *m/z* = 307 (M+1); R_t = 0.4 min.

Example 24 (General procedure (C))

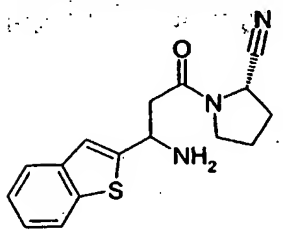
1-(3-(R)-Amino-4-thiophen-3-yl-butyryl)-pyrrolidine-2-(S)-carbonitrile. TFA ()



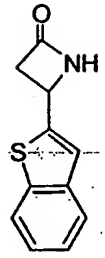
^{1}H NMR (DMSO-d_6): δ 7.90 (m, 3H), 7.54 (m, 1H), 7.35 (m, 1H), 7.06 (m , 1H), 4.74 (t, 1H), 3.75 (s, 1H), 3.53 (m, 1H), 3.29 (m, 1H), 2.93 (m, 2H), 2.58 (m, 2H), 2.16 (m, 2H), 2.01 (m, 2H). HPLC-MS (Method D): *m/z* = 264 (M+1); Rt = 2.89 min.

Example 25 (General procedure (D))

1-(3-Amino-3-benzo[b]thiophen-2-yl-propionyl)-pyrrolidine-2-S-carbonitrile. TFA (25)



Step A: 4-Benzo[b]thiophen-2-yl-azetidin-2-one (25A)

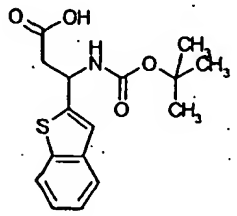


Compound 25A was synthesized in the same manner as described in the general procedure (D) step A from phenylsulfonyl-2-azetidinone (1.0g; 0.47mmol) and 4-benzo[b]thiophene-2-magnesium bromide (0.01 mol). The Grignard analogue was generated from the 2-lithium-4-benzo[b]thiophene by exchange with $MgBr_2$ at RT. 25A was isolated as white crystals. Yield 180mg (19%). Mp = 151.2-151.6 °C.

^{1}H-NMR ($CDCl_3$): δ 3.1(d,t;1H); 3.45(d,d;1H); 4.95(d,d;1H); 6.8(broad s; 1H); 7.2(s;1H); 7.35(m;2H); 7.6-7.8(d,d; 2H). ^{13}C-NMR ($CDCl_3$): δ 47.42; 48.69; 121.70; 121.82; 122.94; 125.03; 125.24; 139.63; 139.77; 145;48; 168:05.

HPLC-MS: (method B): (M+1) = 204; Rt = 2.79min; Purity UV = 90%; Purity TIC = 100%.

Step B: 3-Benzo[b]thiophen-2-yl-3-tert-butoxycarbonylamino-propionic acid (25B)

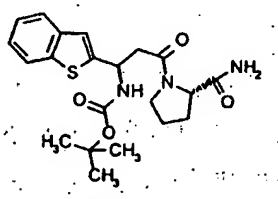


4-Benzo[b]thiophen-2-yl-azetidin-2-one (180mg; 0.89mmol) was dissolved in EtOH/1N NaOH (5:1) (9 ml) the reaction mixture was stirred at RT for 72 hours. $(Boc)_2O$ (1.3 eq.) was added. the reaction was terminated after 16 hours: The reaction mixture was evaporated *in vacuo* dissolved in H_2O (30 ML) by adding 1N HCl until pH = 1; compound 36 precipitated as white crystals. The crystals were washed with water. The acetic water phase was extracted with DCM (3x50 ml) dried with $MgSO_4$ filtered and evaporated *in vacuo* giving 210 mg white crystals. The combined yield was 290mg white crystals (100%).

^{1}H-NMR (CD_3OD): δ 1.45(s;9H); 2.9(d,d; 2H); 4.9(broad s; 3H); 5.4(t;1H); 7.2(s;1H); 7.3(m;2H); 7.7(d,d;1H); 7.8(d,d;1H).

^{13}C-NMR (CD_3OD): δ 29.11; 42.05; 49.82; 81.05; 121.87; 123.55; 124.82; 125.60; 125.73; 140.98; 141.51; 148.5; 174.5; 181.0.

Step C: [1-Benzo[b]thiophen-2-yl-3-(2-S-carbamoyl-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester (25C)

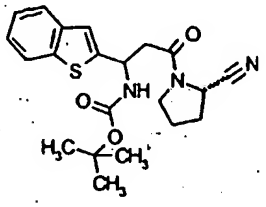


3-Benzo[b]thiophen-2-yl-3-tert-butoxycarbonylamino-propionic acid (0.145g; 0.45mmol) was reacted exactly in the same manner as described in general procedure (D) step C with prolincarboxamide giving compound 25C as an oil. Yield 200mg (100%).

^{1}H-NMR ($CDCl_3$): δ 1.5 (s;9H); 1.75-2.2(m;4H); 2.9(m;1H); 3.4(m;1H); 3.6(m;1H); 4.5(d,t;1H); 5.45(q;1H); 5.9(broad d; 1H); 6.5(t;1H); 6.7(broad d; 1H); 7.15(d;1H); 7.25(m;2H); 7.7(m;2H).

^{13}C-NMR ($CDCl_3$): δ 25.06; 28:73; 36:80; 40:29; 47.96; 53.88; 60.07; 80.18; 120.87; 122.55; 123.77; 124.44; 139.44; 139.94; 147.27; 155.62; 171.3; 173.9; 174.1.

Step D: [1-Benzo[b]thiophen-2-yl-3-(2-S-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester (25D)



[1-Benzo[b]thiophen-2-yl-3-(2-S-carbamoyl-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester (Compound 25C) (0.20g;0.45mmol) was reacted in exactly the same manner as described in the general procedure (D) step D giving compound 25D. Yield 38mg white foam. HPLC-MS (Method B): *m/z* = 420 (M+23); Rt = 4.18min; Purity UV = 98.39; Purity TIC = 100%.

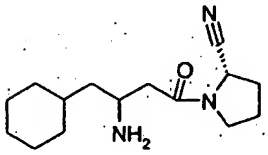
Step E: 1-(3-Amino-3-benzo[b]thiophen-2-yl-propionyl)-pyrrolidine-2-S-carbonitrile. TFA (25)

[1-Benzo[b]thiophen-2-yl-3-(2-S-cyano-pyrrolidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester was reacted in exactly the same manner as described in general procedure (D) step E giving the title compound. Yield: 70 mg (100 %);

^{1}H NMR ($CDCl_3$): δ 1.7-2.2(m;4H); 2.9(d;1H); 3.1-3.6(m;3H); 4.55(m; 1H); 5.15(m;1H); 7.2-7.45(m; 3H); 7.7(d,d;2H); 8.4(broad s; 2H); 13.0(broad s; 1H). ^{13}C NMR ($CDCl_3$): δ 170.5; 139.82; 139.21; 137,64; 125.98; 125.43; 125.30; 124.74; 122.74; 53.82; 48.66; 46.90; 29.95; 28.68; 25.12. HPLC-MS (Method B): *m/z* = 300 (M+1); Rt = 1.68 min; Area UV=100%

Example 26 (General procedure (D))

1-(3-Amino-4-cyclohexyl-butyryl)-pyrrolidine-2-carbonitrile



3-Cyclohexylmethyl-azetidin-2-one;

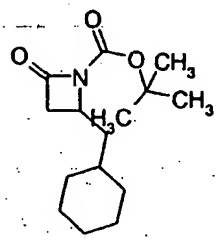
Cyclohexylmethyl magnesium bromide (6.54mmol) in THF was added a solution of 4-Benzenesulfonyl-azidin-2-one (0.552g ; 2.6mmol) in THF (20ml) at – 78°C under nitrogen. The reaction mixture was stirred at -78°C for 30 minutes. The reaction mixture was allowed to warm up for -10°C after 30 min at -10° the reaction was stirred 1 hour at room

temperature. The reaction mixture was purred into a saturated NH_4Cl-water solution (100 ml), and the reaction mixture was evaporated *in vacuo*. The residue was extracted with DCM (4 x 100 ml), dried with $MgSO_4$, filtered and evaporated *in vacuo*. to give an oil, which was purified on a silica gel column. Eluent: (DCM/MeOH) (9:1). The product was isolated as an oil. 180mg.

^{1}H-NMR(CDCl3) d=6.9(broad s; 1H); 3.7(m; 0.5H); 3.4(d; 0.5H); 3.25(d,d,d; 1H); 3.1(m; 1H); 2.85(d,d; 0.5H); 2.55(d,d; 0.5H); 1.7(m; 4H); 1.5(m; 2H); 1.2(m; 4H); 0.9(m; 2H).

LC-MS: M+1= 168; Rt= 3.1min; purity(TIC)=100%.

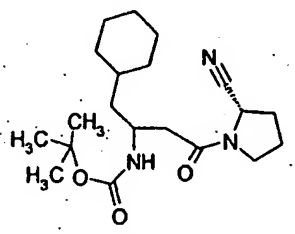
2-Cyclohexylmethyl-4-oxo-azetidine-1-carboxylic acid tert butyl ester;



3-Cyclohexylmethyl-azetidin-2-one (180 mg; 1.08mmol) was dissolved in DCM di-t-butyl dicarbonate ((0.471g; 2.16mmol), TEA (0.327g; 3.24mmol) and DMAP (5mg) were mixed in DCM (10mL) at RT for 144 hours. The reaction mixture was washed with a 5% acetic acid water solution to remove DMAP and TEA. The DCM phase was dried filtered and evaporated *in vaccuo*. The remaining oil was reacted without any purification. 57mg.

^{1}H-NMR(CDCl3): 4.0(m; 0.5H); 3.7(d,d; 0.5H); 3.4(m; 1H); 3.1(d,d,d; 1)H; 2.9(d,d; 0.5H); 2.6(d,d; 0.5H); 1.7(m; 4H); 1.55(two s; 9H); 1.5(m; 2H); 1.25(m; 4H); 1.9(m; 2H).

[3-(2-Cyano-pyrrolidin-1-yl)-1-cyclohexylmethyl-3-oxo-propyl]-carbamic acid tert-butyl ester;



2-Cyclohexylmethyl-4-oxo-azetidine-1-carboxylic acid tert butyl ester (0.056g; 0.21mmol) was added potassium cyanide (0.014g; 0.21mmol); 2-S-cyano pyrrolidine, hydrochloride

(0.044g; 0.21mmol) and TEA (0.021g; 0.21mmol) in DMF. The reaction mixture was heated at 50°C for 16 hours. The reaction mixture was evaporated and purified on prep. Gilson . Yield 27mg oil.

LC-MS: M+23= 387; Rt= 4.29min; purity(TIC)>80%.

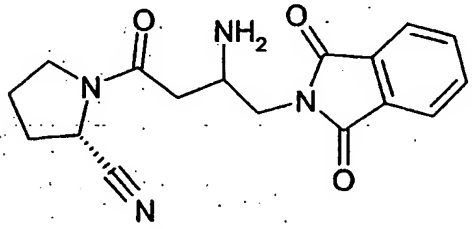
1-(3-Amino-4-cyclohexyl-butyryl)-pyrrolidine-2-S-carbonitrile, TFA;

[3-(2-Cyano-pyrrolidin-1-yl)-1-cyclohexylmethyl-3-oxo-propyl]-carbamic acid tert-butyl ester (0.027g; 0.07mmol) was dissolved in acetonitrile/water 1:1 (4ml) TFA (0.399g; 3.5mmol) was added. The reaction mixture was stirred at room temperature for 24 hours. Evaporation and purification on a prep. Gilson gave the title compound as an oil. 12mg (45%).

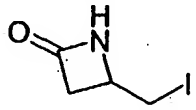
^{1}H-NMR(CDCl3): d 4.7 (d,d, 1H), 4.1 (broad s, 4H), 3.4-3.7 (m, 4H), 2.55 (d, 2H), 2.1-2.3 (m, 4H), 1.5-1.8 (m, 6H), 0.8-1.4 (m, 6H).

Example 27 (General Procedure D)

1-[3-Amino-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyryl]-(S)-pyrrolidine-2-carbonitrile; -1A).



Step A: 4-Iodomethylazetidin-2-one



Allyliodide (71g; 0.423mol) was added drop vice to a cold (-40°C) stirred solution of chlorosulfonylisocyanate (40.6g; 0.287 mol) under nitrogen. After slowly warm up the reaction mixture was stirred at room temperature for 1 week.

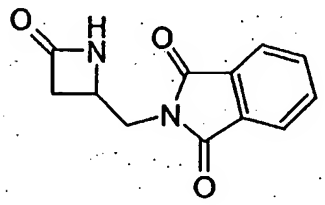
The reaction mixture was slowly purred into a cold (0°C) solution of Na_2SO_3 (52.9g) and $NaHCO_3$ (67.9g) in water (200 ml). Ethyl acetate (200ml) was added and the mixture was stirred for 30 minutes the water phase was extracted with ethyl acetate (3x200ml). The

organic phase was dried with Na_2SO_4, filtered and evaporated *in vaccuo*. The remaining black oil was purified on a silica gel column. Eluent: DCM/MeOH (9:1). Yield 10 g brown-black crystals. Mp= 98-100°C.

^{1}H-NMR: ($CDCl_3$) δ ppm : 6.1(broad s; 1H); 3.9(m; 1H); 3.3(d,d; 2H); 3.1(d,d,d; 1H); 2.2(d,d,d; 2H).

LC-MS: (M+1= 212; Rt= 0.836min; purity (UV)=86%.

2-(4-Oxo-azetidin-2-ylmethyl)-isoindole-1,3-dione;

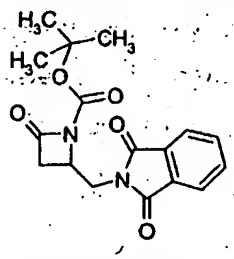


4-Iodomethylazetidin-2-one (1.0g; 4.7mmol) was dissolved in DMF (20 ml) potassium phthalimide (0.96g; 5.2mmol) was added and stirred for 10 days. The reaction mixture was purred into ice water and extracted with DCM (3x30 ml), the organic phase was dried with Na_2SO_4 filtered and evaporated *in vaccuo*. The crude product (1.43g) was purified on a silica gel column. Eluent DCM/MeOH (19:1). Giving 1.2 g impure material. The crystals were purified further on prep. Gilson yield 40 mg white crystals.

^{1}H-NMR($CDCl_3$) 7.85(s; 4H); 7.1(broad s; 0.5H); 3.9(m; 3H); 3.0(d,m; 1H); 2.7(d,d; 1H).

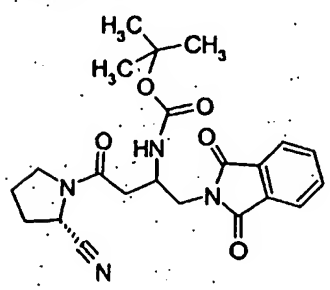
LC-MS: M+23 = 253; M+1= 231; Rt= 1.8min; purity (UV)= 92%.

2-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-4-oxoazetidine-1-carboxylic acid tert butyl ester;



2-(4-Oxo-azetidin-2-ylmethyl)-isoindole-1,3-dione (40mg; 0.17mmol) was dissolved in DCM (10 ml) di-tert.-butyl dicarbonate (45mg; 0.21mmol), TEA (35mg; 0.35mmol) and DMAP (5 mg) were added at room temperature. The reaction mixture was stirred for 16 hours. The reaction mixture was added water (10 ml) the product was extracted with DCM (3x10 ml), dried with $MgSO_4$, filtered evaporate in *vaccuo*. Yield 70 mg oil. The crude product was used in next step without any purification.

[3-(2-(S)-Cyanopyrrolidin-1-yl)-1-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-3-oxopropyl]carbamic acid tert-butyl ester;



2-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-4-oxoazetidine-1-carboxylic acid tert butyl ester(70mg; 0.21mmol) was dissolved in dry DMF(10 ml). Potassium cyanide (14mg; 0.21mmol); 2-S-cyano-pyrrolidine hydrochloride (58 mg; 0.28mmol) and TEA(24mg; 0.23mmol) were added and the reaction mixture was stirred at room temperature for 15 hours. TLC (DCM/MeOH (19:1) showed remaining starting material. The mixture was heated for 50°C for 24 hours. The reaction mixture was added water (20ml) and extracted with DCM (3x20 ml). The combined organic phase was dried with $MgSO_4$ filtered and evaporated *in vaccuo* giving 61 mg oil. The crude product was used without any purification.

1-[3-Amino-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyryl]-pyrrolidine-2-S-carbonitrile, TFA

[3-(2-(S)-Cyanopyrrolidin-1-yl)-1-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-3-oxopropyl]carbamic acid tert-butyl ester(61mg; 0.14mmol) was dissolved in acetonitrile/water (1:1) (10 ml). TFA(0.82g; 7.16 mmol) was added at room temperature. The reaction mixture was stirred for 50 hours. The mixture was evaporated *in vaccuo* and the remaining oil was purified on a prep. Gilson .

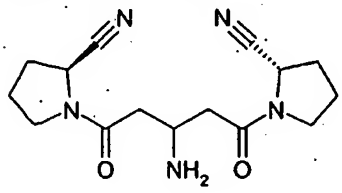
Giving the title compound as the TFA salt. Yield: 35 mg white crystals. Mp: 75.9-76.4°C.

LC-MS: M+1=327; Rt= 0.77min; purity(UV)= 98%.

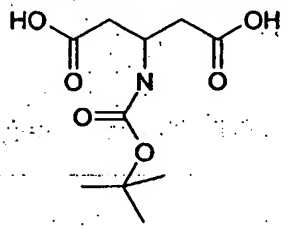
^{1}H-NMR(CDCl3); 9.2(broad s; 1H); 8.4(broad s; 2H); 7.7(m; 4H); 4.7(m; 1H); 4.1(m; 3H); 3.5(m; 2H); 2.9(m; 2H); 2.2(m; 4H).

Example 28

(±) 3-Amino-1,5-(di-2-(S)-cyanopyrrolidin-1-yl)pentane-1,5-dione. TFA



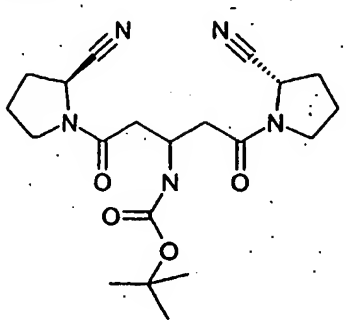
Step A: 3-tert-Butoxycarbonylaminopentanedioic acid



β-Glutamic acid (1.01 g, 6.8 mmol) was dissolved in THF (30 ml) and water (15 ml). Di-tert-butyldicarbonate (2.98 g, 13.6 mmol) and 10% aqueous sodium hydroxide (8.3 ml) were added and the mixture was stirred at room temperature for 5 days. The mixture was evaporated and resuspended in water (30 ml), and then acidified with 1M potassium hydrogen sulphate until pH=2. The aqueous phase was extracted with 2x 60 ml of ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and evaporated to afford 1.5 g (90%) of 3-tert-butoxycarbonylaminopentanedioic acid as white crystals.

^{1}H-NMR (MeOD): δ 1.43(s; 9H); 2.55(d; 4H); 4.25(quin; 1H). HPLC-MS: (method B): m/z: 148 (M+1-Boc).

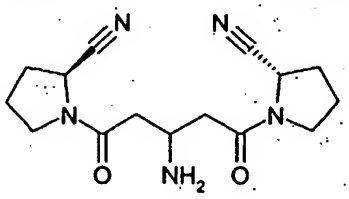
Step B: (±) 3-(1,5-di-(2-(S)-Cyanopyrrolidin-1-yl)pentane)-1,5-dione carbamic acid tert-butyl ester



3-tert-Butoxycarbonylaminopentanedioic acid (0.10 g, 0.4 mmol) was dissolved in DCM (9 ml) and DMF (1 ml). HOAt (0.11 g, 0.81 mmol) and then EDAC (0.16 g, 0.81 mmol) were added at 0°C, and the reaction mixture was stirred for ½ hour at 0°C. Pyrrolidine-2-(S)-carbonitrile (0.17 g, 0.81 mmol) and DIEA (0.21 ml, 1.21 mmol) were added and the mixture was slowly heated to room temperature, and stirred for 3 days. The reaction mixture was evaporated and dissolved in ethyl acetate (50 ml) and water 50 (ml). 1M Potassium hydrogen sulphate (30 ml) was added until pH=2. The organic layer was isolated, and washed with water (10 ml), aqueous sodium hydrogen carbonate (10 ml), and brine (10 ml), and then dried over sodium sulphate, filtered and evaporated, and purified on preparative HPLC (Method A) to afford 85 mg (53%) of (±) 3-(1,5-di-(2-(S)-cyanopyrrolidin-1-yl)pentane)-1,5-dione carbamic acid tert-butyl ester as white crystals.

HPLC-MS: (method B): m/z: 304 (M+1-Boc). Preparative HPLC (Method A): Rt= 9.08 min.

Step C: (±) 3-Amino-1,5-(di-2-(S)-cyanopyrrolidin-1-yl)pentane-1,5-dione. TFA

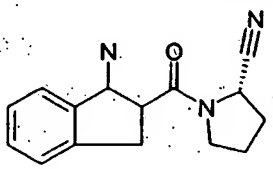


(±) 3-(1,5-di-(2-(S)-Cyanopyrrolidin-1-yl)pentane)-1,5-dione carbamic acid tert-butyl ester (85 mg, 0.21 mmol) was dissolved in water (2 ml) and acetonitrile (2 ml), and TFA (0.8 ml, 10.5 mmol) was added. The reaction mixture was stirred at room temperature for 3 days, and then evaporated, and purified on preparative HPLC (Method A) to afford 69 mg (78%) of (±) 3-amino-1,5-(di-2-(S)-cyanopyrrolidin-1-yl)pentane-1,5-dione, TFA as an oil.

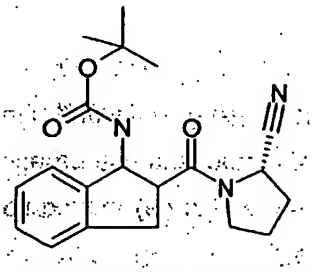
^{1}H-NMR (MeOD): δ 2.05-2.40(m; 8H); 2.77-3.00(m; 4H); 3.51(m; 2H); 3.68(m; 2H); 4.00(m; 1H); 4.78(m; 2H). HPLC-MS: (method B): m/z: 304 (M+1). Preparative HPLC (Method A): Rt= 4.58 min.

Example 29

(+ or -)-Trans-1-(1-aminoindane-2-carbonyl)pyrrolidine-2-(S)-carbonitrile. TFA



Step A: (+ or -) and (- or +)-Trans [2-(2-(S)-cyanopyrrolidine-1-carbonyl)indan-1-yl]carbamic acid tert-butyl ester



(±) trans-1-Aminoindan-2-carboxylic acid, HCL salt (1.34 g, 6.3 mmol) was dissolved in THF 30 ml and water 15 ml. Di-tert-butyldicarbonate (3.15 g, 14.4 mmol) and 2N sodium hydroxide 9.5 ml were added and the mixture was stirred at room temperature for 3 days. The mixture was evaporated and suspended in water 30 ml, and then acidified with 1M potassium hydrogen sulphate until pH=2. The aqueous phase was extracted with 5x 60 ml of ethyl acetate and the combined organic layers were washed with water 100 ml and brine 50 ml, and then dried over sodium sulphate, filtered and evaporated to a yellow oil. The oil was

dried in vacuum to afford 738 mg (42%) of (±) trans-1-tert-butoxycarbonylaminoindan-2-carboxylic acid as yellow crystals. HPLC-MS: (method B): m/z: 300 (M+23).

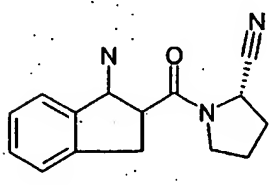
(±) Trans-1-tert-butoxycarbonylaminoindan-2-carboxylic acid (0.39 g, 1.39 mmol) was dissolved in DCM (40 ml). HOBT (0.24 g) and then EDAC (0.8 g, 1.46 mmol) were added at 0°C, and the reaction mixture was stirred for ½ hour at 0°C. Pyrrolidine-2-(S)-carbonitrile (0.29 g, 1.39 mmol) and DIPEA (0.24 ml, 1.39 mmol) were added and the mixture was slowly heated to room temperature, and stirred for 4 days. 1M potassium hydrogen sulphate (30 ml) was added and the organic layer was separated. The aqueous layer was extracted with 3 x 40 ml of DCM and the combined organic layers were washed with sodium hydrogen carbonate (40 ml), water (40 ml) and brine (40 ml), and then dried over sodium sulphate, filtered and evaporated to afford 691 mg of a yellow oil. The diastereomers were separated and purified by flash 12 chromatography (Quad 1, Biotage UK) using ethylacetate:1/heptan:1 as the eluent. Fractions containing the first eluting enantiomer were combined, and evaporated, and dried in vacuum to afford 126 mg (25%) of (+ or -)-trans [2-(2-(S)-cyanopyrrolidine-1-carbonyl)indan-1-yl]carbamic acid tert-butyl ester as white crystals.

^{1}H-NMR ($CDCl_3$): δ 1.43(s;9H); 2.13-2.33(m; 5H); 3.18-3.35(m; 3H); 3.62-3.73(m;2H); 4.88(d;1H); 5.38(br s;1H); 7.23(m;4H). TLC; Rf = 0.30 (EtOAc 1: heptane:1) (first eluting enantiomer). HPLC-MS: (method B): m/z: 378 (M+23).

Fractions containing the second eluting enantiomer were combined, and evaporated, and dried in vacuum to afford 165 mg (33%) of (- or +)-trans [2-(2-(S)-cyanopyrrolidine-1-carbonyl)indan-1-yl]carbamic acid tert-butyl ester as white crystals.

^{1}H-NMR ($CDCl_3$): δ 1.45(s;9H); 2.07-2.40(m; 5H); 3.14-3.90(m; 5H); 4.79(d;1H); 4.95(br s;1H); 7.23(m;4H). TLC; Rf = 0.23 (EtOAc 1: heptane:1) (last eluting enantiomer). HPLC-MS: (method B): m/z: 378 (M+23).

Step B: (+ or -) Trans-1-(1-aminoindane-2-carbonyl)pyrrolidine-2-(S)-carbonitrile. TFA



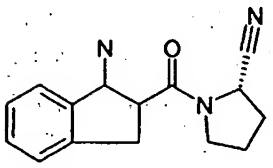
(+ or -)-Trans [2-(2-(S)-cyanopyrrolidine-1-carbonyl)indan-1-yl]carbamic acid tert-butyl ester (0.12 g, 0.34 mmol) was dissolved in water (10 ml) and acetonitrile (10 ml), and TFA (0.39 ml, 5 mmol) was added. The reaction mixture was stirred at room temperature for 3 days, and then evaporated with 3 x 20 ml of toluene. Diethyl ether 10 ml was added and white

crystals was isolated by filtration to afford 108 mg (86%) of (+ or -) trans-1-(1-aminoindane-2-carbonyl)pyrrolidine-2-(S)-carbonitrile. TFA.

^{1}H-NMR (MeOD): δ 2.12-2.33(m; 4H); 3.02(dd; 1H); 3.51(m; 1H); 3.66(m; 2H); 3.82(m;1H); 4.84(m; 1H); 5.28(d; 1H); 7.37(m; 3H); 7.49(d; 1H). HPLC-MS: (method B): m/z: 256 (M+1).

Example 30

(- or +) Trans-1-(1-aminoindane-2-carbonyl)pyrrolidine-2-(S)-carbonitrile. TFA

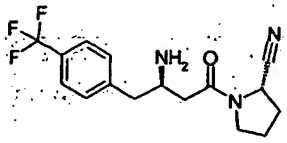


(- or +)-Trans-[2-(2-(S)-cyanopyrrolidine-1-carbonyl)indan-1-yl]carbamic acid tert-butyl ester (0.16 g, 0.45 mmol) was dissolved in water (10 ml) and acetonitrile (10 ml), and TFA (0.34 ml, 4.5 mmol) was added. The reaction mixture was stirred at room temperature for 5 days, and then evaporated with 3 x 20 ml of toluene. Diethyl ether 10 ml was added and white crystals was isolated by filtration to afford 124 mg (75%) of (- or +) trans-1-(1-aminoindane-2-carbonyl)pyrrolidine-2-(S)-carbonitrile, TFA.

^{1}H-NMR (MeOD): δ 2.12-2.40(m; 4H); 3.01(dd; 1H); 3.60(m; 3H); 3.85(m; 1H); 4.78(m; 1H); 5.32(d; 1H); 7.34(m; 3H); 7.50(d; 1H). HPLC-MS: (method B): m/z: 256 (M+1).

Example 31 (General procedure (C))

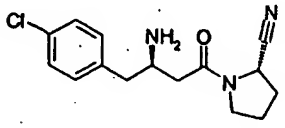
1-[3-(R)-Amino-4-(4-trifluoromethyl-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**31**)



^{1}H NMR (DMSO-d_6): δ 7.89 (m, 3H), 7.73 (d, 2H), 7.52 (d, 2H), 4.73 (t, 1H), 3.79 (m, 1H), 3.45 (m, 2H), 3.00 (m, 2H), 2.63 (m, 2H), 2.15 (m, 2H), 2.00 (m, 2H). HPLC-MS (Method D): *m/z* = 326 (M + 1); Rt = 3.83 min.

Example 32 (General procedure (C))

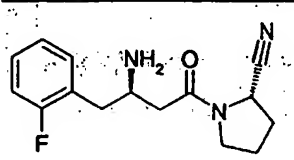
1-[3-(R)-Amino-4-(4-chloro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**32**)



^{1}H NMR (DMSO-d_6): δ 7.91 (s, 3H), 7.42 (d, 2H), 7.31 (d, 2H), 4.74 (t, 1H), 3.73 (s, 1H), 3.54 (m, 1H), 3.31 (m, 1H), 2.91 (m, 2H), 2.58 (m, 2H), 2.15 (m, 2H), 2.01 (m, 2H). HPLC-MS (Method D): *m/z* = 292 (M + 1); Rt = 3.73 min.

Example 33 (General procedure (C))

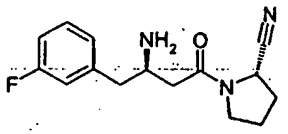
1-[3-(R)-Amino-4-(2-fluoro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**33**)



^{1}H NMR (DMSO-d_6): δ 7.95 (s, 3H), 7.40 (m, 1H), 7.12 (m, 3H), 4.74 (t, 1H), 3.78 (m, 1H), 3.54 (m, 1H), 3.32 (m, 1H), 2.94 (m, 2H), 2.60 (m, 2H), 2.15 (m, 2H), 2.01 (m, 2H). HPLC-MS (Method D): *m/z* = 276 (M + 1); Rt = 3.30 min.

Example 34 (General procedure (C))

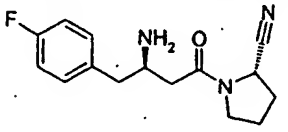
1-[3-(R)-Amino-4-(3-fluoro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**34**)



^{1}H NMR (DMSO-d_6): δ 8.01 (s, 3H), 7.36 (m, 2H), 7.21 (m, 2H), 4.73 (t, 1H), 3.76 (m, 1H), 3.48 (m, 1H), 3.41 (m, 1H), 2.92 (m, 2H), 2.61 (m, 2H), 2.18 (m, 2H), 1.98 (m. 2H). HPLC-MS (Method D): *m/z* = 276 (M + 1); Rt = 3.38 min.

Example 35 (General procedure (C))

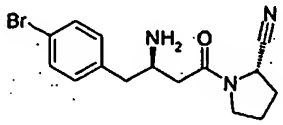
1-[3-(R)-Amino-4-(4-fluoro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**35**)



^{1}H NMR (DMSO-d_6): δ 7.90 (s, 3H), 7.31 (m, 2H), 7.18 (m, 2H), 4.74 (t, 1H), 3.73 (s, 1H), 3.55 (m, 1H), 3.31 (m, 1H), 2.95 (m, 1H), 2.84 (m, 1H), 2.58 (m, 2H), 2.16 (m, 2H), 2.01 (m, 2H). HPLC-MS (Method D): *m/z* = 276 (M + 1); Rt = 3.47 min.

Example 36 (General procedure (C))

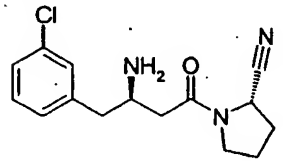
1-[3-(R)-Amino-4-(4-bromo-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**36**)



^{1}H NMR (DMSO-d_6): δ 7.92 (s, 3H), 7.55 (d, 2H), 7.25 (d, 2H), 4.74 (t, 1H), 3.74 (s, 1H), 3.55 (m, 1H), 3.31 (m, 1H), 2.89 (m, 2H), 2.59 (m, 2H), 2.16 (m, 2H), 2.01 (m, 2H). HPLC-MS (Method D): *m/z* = 336 (M + 1); Rt = 3.88 min.

Example 37 (General procedure (C))

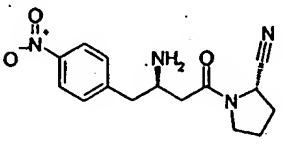
1-[3-(R)-Amino-4-(3-chloro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**37**)



^{1}H NMR (DMSO-d_6): δ 7.95 (s, 3H), 7.31 (m, 3H), 7.26 (m, 1H), 4.74 (t, 1H), 3.78 (s, 1H), 3.56 (m, 1H), 3.32 (q, 1H), 2.93 (m, 2H), 2.60 (m, 2H), 2.16 (m, 2H), 2.02 (m, 2H). HPLC-MS (Method D): *m/z* = 292 (M + 1); Rt = 3.66 min.

Example 38 (General procedure (C))

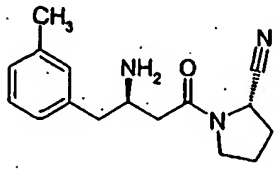
1-[3-(R)-Amino-4-(4-nitro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**38**)



^{1}H NMR (DMSO-d_6): δ 8.22 (d, 2H), 8.01 (s, 3H), 7.58 (d, 2H), 4.72 (t, 1H), 3.84 (s, 1H), 3.55 (m, 1H), 3.54 (m, 1H), 3.07 (m, 2H), 2.66 (m, 2H), 2.16 m, 2H), 2.01 (m, 2H). HPLC-MS (Method D): *m/z* = 303 (M + 1); Rt = 3.19 min.

Example 39 (General procedure (C))

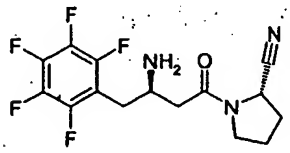
1-(3-(R)-Amino-4-m-tolyl-butyryl)-pyrrolidine-2-(S)-carbonitrile. TFA (**39**)



^{1}H NMR (DMSO-d_6): δ 7.81 (s, 3H), 7.24 (m, 1H), 7.07 (m, 3H), 4.75 (m, 1H), 3.72 (s, 1H), 3.51 (m, 1H), 3.32 (q, 1H), 2.92 (m, 2H), 2.79 (m, 2H), 2.16 (m, 2H), 2.02 (m, 2H). HPLC-MS (Method D): *m/z* = 272 (M + 1); Rt = 3.46 min.

Example 40 (General procedure (C))

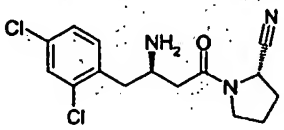
1-(3-(R)-Amino-4-pentafluorophenyl-butyryl)-pyrrolidine-2-(S)-carbonitrile. TFA (**40**)



^{1}H NMR (DMSO-d_6): δ 8.11 (s, 3H), 4.69 (m, 1H), 3.67 (s, 1H), 3.51 (m, 1H), 3.37 (m, 1H), 3.07 (m, 2H), 2.69 (m, 2H), 2.13 (m, 2H), 2.02 (m, 2H). HPLC-MS (Method D): *m/z* = 348 (M + 1); Rt = 3.59 min.

Example 41 (General procedure (C))

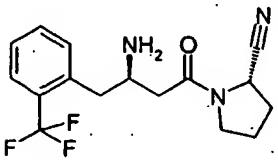
1-[3-(R)-Amino-4-(2,4-dichloro-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**41**)



^{1}H NMR (DMSO-d_6): δ 8.01 (s, 3H), 7.64 (m, 1H), 7.44 (m, 2H), 4.74 (t, 1H), 3.80 (m, 1H), 3.56 (m, 1H), 3.32 (m, 1H), 3.04 (m, 2H), 2.64 (m, 2H), 2.20 (m, 2H), 1.98 (m, 2H). HPLC-MS (Method D): *m/z* = 326; Rt = 3.79 min.

Example 42 (General procedure (C))

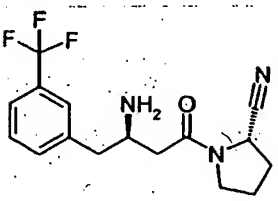
1-[3-(R)-Amino-4-(2-trifluoromethyl-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**42**)



^{1}H NMR (DMSO-d_6): δ 8.06 (s, 3H), 7.63 (m, 4H), 4.73 (t, 1H), 3.86 (s, 1H), 3.53 (m, 1H), 3.32 (m, 1H), 3.20 (m, 1H), 3.08 (m, 1H), 2.63 (m, 2H), 2.19 (m, 2H), 1.97 (m, 2H). HPLC-MS (Method D): *m/z* = 326 (M + 1); Rt = 3.59 min.

Example 43 (General procedure (C))

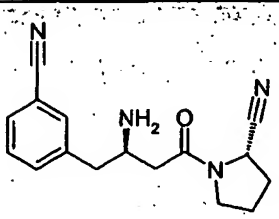
1-[3-(R)-Amino-4-(3-trifluoromethyl-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**43**)



^{1}H NMR (DMSO-d_6): δ 7.97 (s, 3H), 7.62 (m, 4H), 4.74 (t, 1H), 3.82 (s, 1H), 3.56 (m, 1H), 3.34 (m, 1H), 3.01 (m, 2H), 2.62 (m, 2H), 2.16 (m, 2H), 2.02 (m, 2H). HPLC-MS (Method D): *m/z* = 326 (M + 1); Rt = 3.76 min.

Example 44 (General procedure (C))

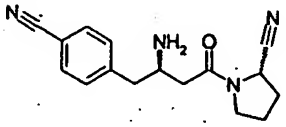
1-[3-(R)-Amino-4-(3-cyano-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (**44**)



^{1}H NMR (DMSO-d_6): δ 7.93 (m, 3H), 7.77 (2H), 7.60 (m, 2H), 4.74 (t, 1H), 3.81 (s, 1H), 3.57 (m, 1H), 3.28 (m, 1H), 2.96 (m, 2H), 2.64 (m, 2H), 2.16 (m, 2H), 2.00 (m, 2H) HPLC-MS (Method D): *m/z* = 283 (M + 1); Rt = 2.99 min.

Example 45 (General procedure (C))

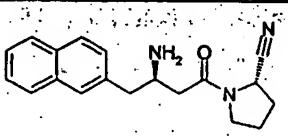
1-[3-(R)-Amino-4-(4-cyano-phenyl)-butyryl]-pyrrolidine-2-(S)-carbonitrile. TFA (45)



^{1}H NMR (DMSO-d_6): δ 7.95 (s, 3H), 7.83 (d, 2H), 7.51 (d, 2H), 4.73 (t, 1H), 3.81 (s, 1H), 3.56 (m, 1H), 3.31 (m, 1H), 2.99 (m, 2H), 2.62 (m, 2H), 2.20 (m, 2H), 1.98 (m, 2H). HPLC-MS (Method D): *m/z* = 283 (M + 1); Rt = 3.03 min.

Example 46 (General procedure (C))

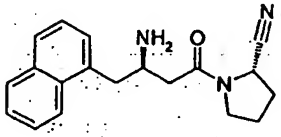
1-(3-(R)-Amino-4-naphthalen-2-yl-butyryl)-pyrrolidine-2-(S)-carbonitrile. TFA (46)



^{1}H NMR (DMSO-d_6): δ 8.00-7.85 (m, 6H); 7.82-7.77 (m, 1H); 7.56 7.48 (m, 2H); 7.44 (d, 1H); 4.76 (t, 1H); 3.87 (s br, 1H); 3.27 (q, 1H); 3.14 (dd, 1H); 3.04 (dd, 1H); 2.66-2.60 (m, 1H); 2.20 -2.10 (m, 2H); 2.04-1.90 (m, 2H). HPLC-MS (Method D): *m/z* = 308 (M + 1); Rt = 3.79 min.

Example 47 (General procedure (C))

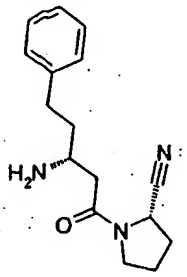
1-(3-(R)-Amino-4-naphthalen-1-yl-butyryl)-pyrrolidine-2-(S)-carbonitrile. TFA (47)



^{1}H NMR (DMSO-d_6): δ 8.25-8.19 (m, 1H); 8.00-7.87 (m, 5H); 7.65-7.40 (m, 4H); 4.77 (t, 1H); 3.83 (s br, 1H); 3.54-3.48 (m, 1H) 3.31-3.22 (m, 1H); 2.70-2.63 (m, 1H); 2.30-2.10 (m, 2H); 2.08-1.88 (m, 2H). HPLC-MS (Method D): *m/z* = 308 (M + 1); Rt = 3.73 min.

Example 48

1-(3-(R)-Amino-5-phenyl-pentanoyl)-pyrrolidine-(2S)-carbonitrile. TFA (48)



Step A: [3-(2-(S)-Carbamoyl-pyrrolidin-1-yl)-3-oxo-1-(R)-phenethyl-propyl]-carbamic acid *tert* butyl ester (48A)

N-Boc-3-(R)-amino-5-phenylpentanoic acid (Aldrich) (10 g, 34 mmol) was dissolved in DCM (300 ml) at 0°. HOAt (4.64 g, 34 mmol) was added, and the solution stirred for 30 min at 0°. EDAC (6.53 g, 34 mmol) was added, and stirring continued for 2½ hours at 0°. L-Prolinamide (3.89 g, 34 mmol) was added, followed by DIEA (5.84 ml, 34 mmol), and the stirring continued while the reaction was allowed to warm to room temperature. After six days of stirring the reaction mixture was added to a 1M $KHSO_4$ solution, stirred for 1 hour, the phases separated, and the aqueous phase extracted with DCM (2 x 200 ml). The combined organic extract was washed saturated $NaHCO_3$ (2 x 200 ml), and brine (100 ml), dried with Na_2SO_4 and evaporated to give12.09 g of compound 48A.

^1H NMR ($CDCl_3$): δ 7.23 (m, 5H); 6.92 (s, 1H); 5.31 (m, 2H); 4.56 (m, 1H); 3.96 (m, 1H); 3.45 (m, 2H); 2.63 (m, 4H); 2.08 (m, 6H); 1.43 (s, 9H);

Step B: [3-(2-(S)-Cyano-pyrrolidin-1-yl)-3-oxo-1-(R)-phenethyl-propyl]-carbamic acid tert butyl ester (48B)

[3-(2-(S)-Carbamoyl-pyrrolidin-1-yl)-3-oxo-1-(R)-phenethyl-propyl]-carbamic acid *tert* butyl ester (12 g, 30.8 mmol) was dissolved in dry pyridine (120 ml) and cooled to 0°, with stirring. Phosphorous oxychloride (4.23 ml, 46.2 mmol) was slowly added at 0°, and the stirring continued for 30 min. Ice water was carefully added, followed by EtOAc, and the reaction stirred until it reached room temperature. The phases were separated, and the aqueous phase extracted with EtOAc (3 x 200 ml). The combined organic extracts were washed with water (200 ml), and brine (200 ml), dried with Na_2SO_4, and evaporated to give 12.6 g of impure product, which was further purified by column chromatography on silica gel (70-230 mesh, 1 litre), using 5 % MeOH in DCM as eluent, to give 8.2 g of compound 19B.

^{1}H NMR ($CDCl_3$): δ 7.23 (m, 5H); 5.43 (m, 1H); 4.67 (m, 1H); 3.92 (m, 1H); 3.47 (m, 2H); 2.66 (m, 4H); 2.06 (m, 6H); 1.43 (s, 9H);

Step C 1-(3-(R)-Amino-5-phenyl-pentanoyl)-pyrrolidine-2-(S)-carbonitrile. TFA (48)

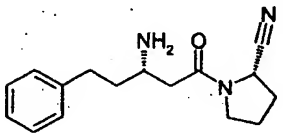
[3-(2-(S)-Cyano-pyrrolidin-1-yl)-3-oxo-1-(R)-phenethyl-propyl]-carbamic acid tert butyl ester (3.54 g, 9.53 mmol) was dissolved in MeCN (75 ml) and water (75 ml), and TFA was added (36.6 ml, 476 mmol). The reaction was stirred for 2 days, and evaporated to a yellow oil. The oil was dissolved in water and DCM (1+1), and the aqueous phase evaporated, and vacuum dried for 3 days, redissolved in water (50 ml), and freeze dried to give the title compound (3.0 g) as a white hygroscopic powder.

^{1}H NMR (MeOH-d_4): δ 7.24 (m, 5H); 4.77 (m, 1H); 3.56 (m, 3H); 2.74 (m, 4H); 2.16 (m, 6H).

HPLC-MS (Method B): m/z = 272 (M + 1); Rt = 1.96 min.

Example 49

1-(3-(S)-Amino-5-phenyl-pentanoyl)-pyrrolidine-2-(S)-carbonitrile. TFA (49)



Step A: [3-(2-(S)-Carbamoyl-pyrrolidin-1-yl)-3-oxo-1-(S)-phenethyl-propyl]-carbamic acid *tert* butyl ester (49A)

N-Boc-3-(S)-amino-5-phenylpentanoic acid was reacted with L-prolinamide as described in Example 48, step A to afford 915 mg of compound 49A as white crystals in 79 % yield. Mp. 54 - 60°C.

^{1}H NMR ($CDCl_3$): δ 7.23 (m, 5H); 6.98 (br. s, 1H); 5.35 (m, 2H); 4.56 (m, 1H); 3.96 (m, 1H); 3.45 (m, 2H); 2. 63 (m, 4H); 1.94 (m, 6H); 1.43 (s, 9H);

Step B: [3-(2-(S)-Cyano-pyrrolidin-1-yl)-3-oxo-1-(S)-phenethyl-propyl]-carbamic acid tert butyl ester (49B)

[3-(2-(S)-Carbamoyl-pyrrolidin-1-yl)-3-oxo-1-(S)-phenethyl-propyl]-carbamic acid *tert* butyl ester (12 g, 30.8 mmol) was reacted as described in Example 48 step B to afford 530 mg of compound 49B as a yellow oil in 71 % yield.

^{1}H NMR ($CDCl_3$): δ 7.23 (m, 5H); 5.47 (m, 1H); 4.68 (m, 1H); 3.92 (m, 1H); 3.47 (m, 2H); 2.66 (m, 4H); 2.06 (m, 6H); 1.43 (s, 9H);

Step C 1-(3-(S)-Amino-5-phenyl-pentanoyl)-pyrrolidine-2-(S)-carbonitrile. TFA (49)

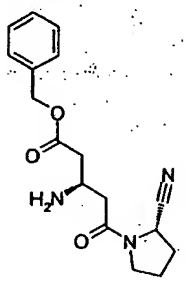
[3-(2-(S)-Cyano-pyrrolidin-1-yl)-3-oxo-1-(S)-phenethyl-propyl]-carbamic acid tert butyl ester was reacted as described in Example 48 step C to afford 320 mg of the title compound as a yellow oil in 61 % yield.

^{1}H NMR (MeOH-d_4): δ 7.24 (m, 5H); 4.78 (m 1H); 3.56 (m 3H); 2.74 (m, 4H); 2.16 (m, 6H).

HPLC-MS (Method B): m/z = 272 (M + 1); Rt = 1.79 min

Example 50

3-(R)-Amino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxopentanoic acid benzyl ester. TFA (50)



Step A: 3-(R)-tert-Butoxycarbonylamino-5-(2-(S)-carbamoylpyrrolidin-1-yl)-5-oxo-pentanoic acid benzyl ester (50A)

3-(R)-tert-Butoxycarbonylaminopentanedioic acid monobenzyl ester (Fluka) (1.01 g, 2.99 mmol) was reacted with L-prolineamide as described in example 48, step A to afford 1.28 g of compound 50A as white crystals in 98 % yield.

^{1}H NMR ($CDCl_3$): δ 7.35 (m, 5H); 6.97 (br. s, 1H); 5.83 (br. s, 1H); 5.28 (br. s, 1H); 5.13 (d, 1H); 5.09 (d, 1H); 4.53 (dd, 1H); 4.32 (m, 1H); 3.31 (m, 2H); 2.89-2.48 (m, 4H); 2.35 (m, 1H); 1.94 (m, 3H); 1.42 (s, 9H).

Step B: 3-(R)-tert-Butoxycarbonylamino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxo-pentanoic acid benzyl ester (50B)

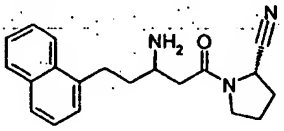
3-(R)-tert-Butoxycarbonylamino-5-(2-(S)-carbamoylpyrrolidin-1-yl)-5-oxo-pentanoic acid benzyl ester (81 mg, 0.19 mmol) was reacted as described in example 48 step B, and the crude product was purified by preparative HPLC (method A), to afford 56 mg of compound 50B as a clear oil in 72 % yield.
HPLC-MS (Method B): m/z = 316 (M + 1 - Boc); Rt = 3.85min; Purity UV = 100 %.

Step C 3-(R)-Amino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxopentanoic acid benzyl ester. TFA (50)

3-(R)-tert-Butoxycarbonylamino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxo-pentanoic acid benzyl ester (56 mg, 0.14 mmol) was reacted with trifluoroacetic acid as described in example 48 step C, and purified by preparative HPLC (method A), to afford 36 mg of the title compound as an yellow oil in 62 % yield.
^{1}H NMR (MeOH-d_4): δ 7.34 (m, 5H); 5.20 (s, 2H); 5.75 (dd, 1H); 3.98 (m, 1H); 3.58 (m, 1H); 3.45 (m, 1H); 2.83 (m, 4H); 2.19 (m, 4H). HPLC-MS (Method B): *m/z* = 316 (M + 1); Rt = 1.77min; Purity UV = 63.4 %.

Example 51

1-(3-Amino-5-naphthalen-1-yl-pentanoyl)-pyrrolidine-2-carbonitrile. TFA (51)



Step A: 4-(2-Naphthalen-1-yl-ethyl)-azetidin-2-one (51A)

(Phenylsulfonyl)-2-azetidinone (1.5 g; 7.1 mmol) was dissolved in dry THF (50 ml) cooled to –78 °C under N_2. 2-Naphthalen-1-ethyl magnesium chloride in THF (14.2 mmol) was added keeping the temperature below -60 °C. The reaction mixture was stirred at -78 °C for ~30 min. then allowed to warm up 0 °C and kept at 0 °C for 30 min. A saturated NH_4Cl-water solution (100 ml) was added. The reaction mixture was evaporated *in vacuo*. The residue was extracted with DCM (3 x 75 ml), dried with $MgSO_4$, filtered, and evaporated *in*

vacuo to oil, which was purified by prep. HPLC (method A), to give 0.25 g (16 %) of compound 51A, as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.0 (q, 2H); 2.45 (dd, 1H); 2.95 (dt, 1H); 3.05 (m, 2H); 3.55 (m,1H); 6,5 (broad s, 1H); 7.2-7.5 (m, 4H); 7.65 (d,1H); 7.8 (dd, 1H); 7.9 (dd,1H).

^{13}C-NMR ($CDCl_3$) δ: 30.27, 36.61, 43.77, 48:41, 123.84, 125.95, 126.10, 126.40, 127.58, 129.36, 131.98, 134.32, 135.01, 137.17, 168.95.

Step B: 3-tert-Butoxycarbonylamino-5-naphthalen-1-yl-pentanoic acid (51B)

4-(2-Naphthalen-1-yl-ethyl)-azetidin-2-one (0.25 g; 1.1 mmol) was dissolved in 1N NaOH:EtOH (15:50 ml). The reaction mixture was stirred at room temperature for 16 hours. $(Boc)_2O$ (1.3 eq.) was added, and the reaction was stirred 16 hours. The reaction mixture was evaporated *in vacuo*, dissolved in water, and pH was adjusted to 1-2 with 1N HCl. The mixture was extracted with DCM (3 x 100 ml). The organic phase was dried, filtered and evaporated *in vacuo*. The remaining oil was purified by prep. HPLC (method A), to give 300 mg (79 %) of compound 51B as white crystals. Mp: 143-144.7 °C.

^{1}H-NMR (MeOH-d_4): δ 1.5 (s, 9H); 1.9 (m, 2H); 2.5 (dd, 2H); 3.05-3.25 (m, 2H); 4.05 (m,1H); 5.0 (s, 2H); 7.25-7.55 (m, 4H); 7.65 (d, 1H); 7.8 (d, 1H); 8.05 (d, 1H).

Step C: [3-(2-S-Carbamoyl-pyrrolidin-1-yl)-1-(2-naphthalen-1-yl-ethyl)-3-oxo-propyl]-carbamic acid tert-butyl ester (51C)

3-tert-Butoxycarbonylamino-5-naphthalen-1-yl-pentanoic acid (0.159 g;0.44 mmol) was dissolved in DMF (30 ml), and added HOBt (0.15; 0.44 mmol), EDAC (0.126 g; 0.66 mmol), and finally L-Prolinamide (0.050 g; 0.44 mmol). The mixture was stirred at room temperature for 2.5 hours. The mixture was evaporated *in vacuo*, and the remaining oil was dissolved in DCM (75 ml), and washed with 1N NaOH (50 ml), 5 % acetic acid (50 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residual oil was purified by prep. HPLC (method A), to give 0.14 g (73 %) of compound 51C.

HPLC-MS (method B): *m/z* = 340 (M - Boc+1); Rt = 3.89 min; purity TIC = 100 %.

Step D: [3-(2-S-Cyano-pyrrolidin-1-yl)-1-(2-naphthalen-1-yl-ethyl)-3-oxo-propyl]-carbamic acid tert-butyl ester (51D)

[3-(2-S-Carbamoyl-pyrrolidin-1-yl)-1-(2-naphthalen-1-yl-ethyl)-3-oxo-propyl]-carbamic acid tert-butyl ester (0.140 g; 0.319 mmol) was dissolved in DCM (3 ml) and cooled to 0° on ice. Pyridine (0.379 g; 4.79 mmol) was added, and then phosphorous oxychloride (0.196 g; 1.28 mmol) was added slowly. The reaction mixture was stirred at 0° C for 4 hours. The reaction was poured onto ice, and extracted with DCM (2 x 6 ml). The DCM phase was washed with saturated $NaHSO_4$ (2 ml), $NaHCO_3$ (2 ml), and brine (2 ml), dried with $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by prep. HPLC (method A) to give 90 mg (67 %) of compound 51D.

HPLC-MS (method B): *m/z* = 322 (M – Boc + 1); Rt = 4.62min; purity UV = 96.96 %; purity TIC = 100 %

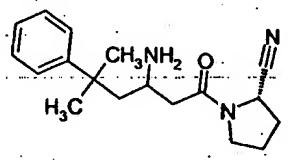
Step E: 1-(3-Amino-5-naphthalen-1-yl-pentanoyl)-pyrrolidine-2-(S)-carbonitrile. TFA (51)

[3-(2-S-Cyano-pyrrolidin-1-yl)-1-(2-naphthalen-1-yl-ethyl)-3-oxo-propyl]-carbamic acid tert-butyl ester (0.09 g; 0.21 mmol) was dissolved in DCM (10 ml). TFA (1 ml) was added, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated *in vacuo*, and the residual oil was purified by prep. HPLC (method A), to give the 17 mg (19 %) of the title compound.

HPLC (method A): Rt = 7.79 min; purity = 98.6 %.

Example 52

(S)-1-(3-Amino-5-methyl-5-phenylhexanoyl)pyrrolidine-2-carbonitrile. TFA (52)



Step A: 4-(2-Methyl-2-phenyl-propyl)-azetidin-2-one (52A)

(Phenylsulfonyl)-2-azetidinone (1.0 g; 0.47 mmol) was dissolved in dry THF (50 ml) cooled to –78 °C under N_2. 2-Methyl-2-phenylpropylmagnesium chloride in diethyl ether (0.5 M) (20 ml; 0.95 mmol) was added keeping the temperature below –60 °C. The reaction mixture was allowed to warm up to 0 °C kept at 0 °C for 30 min, and then stirred at room temperature for 15 hours under N_2. A saturated NH_4Cl-water solution (100 ml) was added, and the reaction mixture was evaporated *in vacuo*. The residue was extracted with DCM (4 x 100 ml), dried with $MgSO_4$, filtered and evaporated *in vacuo*. to give an oil, which was purified by prep. HPLC (method A) to give 250 mg (26 %) of compound 52A as an oil.

HPLC-MS (method B): (M + 1) = 204; Rt = 3.64 min; purity: TIC = 95 %.

^{1}H-NMR ($CDCl_3$): δ: 1.35 (2s, 6H); 1.9 (dd, 2H); 2.4 (dd, 1H); 2.9 (dt,1H); 3.5 (m, 1H); 5.5 (broad s, 1H); 7.35(m, 5H).

^{13}C-NMR ($CDCl_3$) δ: 28.11, 30.28, 37.65, 44.63, 45.93, 50.39, 126.18, 126.38, 126.51, 128.59, 128.75, 147.72, 168.65.

Step B: 3-tert-Butoxycarbonylamino-5-methyl-5-phenyl-hexanoic acid (52B)

4-(2-Methyl-2-phenyl-propyl)-azetidin-2-one (0.25 g, 1.23 mmol) was reacted and purified as described in step B, example 51, giving 180 mg (46 %) of compound 52B, as an oil.

HPLC-MS (method B): *m/z* = 344 (M+23); Rt = 4.44 min; purity: UV = 96 %.

Step C: {1-[2-(2-(S)-Carbamoylpyrrolidin-1-yl)-2-oxoethyl]-3-methyl-3-phenylbutyl}carbamic acid tert-butyl ester (52C)

3-tert-Butoxycarbonylamino-5-methyl-5-phenyl-hexanoic acid and L-prolineamide was reacted and purified as described in step C, example 51, giving 82 mg (70 %) of compound 52C as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.3 (m, 5H); 1.7-2.35 (m, 7H); 3.15 (m,1H); 3.9 (broad s, 1H); 4.45 (m, 1H); 5.1 (m,1H); 5.8 (d, 1H); 6.9-7.1 (m,2H); 7.3 (m, 5H).

Step D: {1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-methyl-3-phenylbutyl}carbamic acid tert-butyl ester (52D)

{1-[2-(2-(S)-Carbamoylpyrrolidin-1-yl)-2-oxoethyl]-3-methyl-3-phenylbutyl}carbamic acid tert-butyl ester was reacted and purified as described in step D, example 51, giving 53 mg (66 %) of compound 52D as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (m,15H); 1.9-2.3 (m,7H); 2.7-3.3 (m,2H); 3.85 (m,1H); 4.1 (m,1H); 5.3 (m,1H); 7.2 (m,1H); 7.25-7.4 (m,5H).

Step E: 1-(3-Amino-5-methyl-5-phenylhexanoyl)pyrrolidine-2-(S)-carbonitrile. TFA (52)

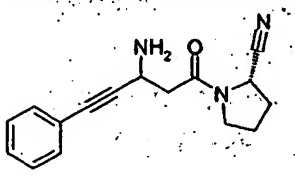
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-methyl-3-phenylbutyl}carbamic acid tert-butyl ester (53 mg, 0.133 mmol) was dissolved in MeCN:water (1:1) (2 ml). TFA (0.76 g;

6.6 mmol) was added at room temperature. The reaction mixture was stirred for 48 hours. Evaporation gave 45 mg (84 %) of the title compound as oil.

^{1}H NMR ($CDCl_3$): δ 1.35 (s, 3H); 1.45 (s, 3H); 1.9-2.1 (m, 6H); 2.4 (m, 0.5H); 2.8 (m, 1.5H); 2.95 (m, 0.5H); 4.55 (m, 0.5H); 7.2-7.6 (m, 6H); 9.6 (broad s, 2H). HPLC-MS (Method B): *m/z* = 300 (M + 1); Rt = 2.20 min.

Example 53

(S)-1-(3-Amino-5-phenylpent-4-ynoyl)pyrrolidine-2-carbonitrile. TFA (53)



Step A: 4-Phenylethynyl-azetidin-2-one (53A)

Phenylacetylen (3.87 g; 37.9 mmol) was dissolved in dry THF (20 ml). Ethylmagnesiumbromide (3 M) in tert-butylmethyl ether (37.9 ml) was added under N2 at -40 °C. The Grignard salt of phenylacetylene precipitated. THF (30 ml) was added and the reaction was stirred at RT for 30 min. The reaction mixture was cooled to -40 °C and a solution of phenylsulfonyl-2-azetidinone (2.0 g; 0.95 mmol) in THF (30 ml) was added. The mixture was allowed to warm up to RT and stirred for 1.5 hour. 1 N HCl (50 ml) was added and the reaction mixture extracted with DCM (3 x 100 ml). The organic phase was dried, filtered, and evaporated *in vacuo* to give 2.5 g oil, which was purified on a silica gel column with DCM:MeOH (19:1) as eluent, to give compound 53A. Yield 0.6 g (37 %) white crystals. Mp = 103.2 - 103.6 °C.

HPLC-MS (Method B): m/z = 172 (M + 1); Rt = 2.70min; Purity UV = 99.42 %; Purity TIC = 100 %.

^{1}H-NMR ($CDCl_3$): δ 3.15(d,d,d;1H);3.4(d,d,d;1H); 4.45(d,d; 1H); 6.9(broad s; 1H); 7.3(m;3H); 7.45(m;2H).

^{13}C-NMR ($CDCl_3$): δ 38.02; 47.13; 85.25; 87.28; 122.43; 128.78; 129.14; 132.08; 167.91.

Step B: 3-tert-Butoxycarbonylamino-5-phenyl-pent-4-ynoic acid (53B)

4-Phenylethynyl-azetidin-2-one (0.60 g; 3.5 mmol) was dissolved in 1N NaOH:EtOH (15:50 ml). The reaction mixture was stirred at room temperature for 16 hours. $(Boc)_2O$ (1.3 eq.) was added and the reaction was stirred for 120 hours. The reaction mixture was

evaporated *in vacuo* and dissolved in water, and pH adjusted to 1-2. The mixture was extracted with DCM (3 x 100 ml). The organic phase was dried, filtered, and evaporated *in vacuo*. The remaining oil was purified by prep. HPLC (method A), to give compound 53B as an oil. Yield 0.446 g (44 %).

^{1}H-NMR ($CDCl_3$):δ 1.5(s; 9H); 2.7(d,d;1H); 4.9(m;2H); 7.25-7.45(m; 5H).

Step C: (S)-{1-[2-(2-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-phenylprop-2-ynyl}carbamic acid tert-butyl ester (53C)

3-tert-Butoxycarbonylamino-5-phenyl-pent-4-ynoic acid (0.446 g; 1.54 mmol) was dissolved in DMF (20 ml). HOBt (0.238 g; 1.56 mmol), EDAC (0.31 g; 1.05 mmol), and TEA (0.178 g;1.14 mmol) were added, and after 15 minutes 0.349g; 1.66mmol 2-(S)-cyanopyrrolidine. TFA was added. The reaction mixture was stirred at room temperature for 16 hours, evaporated *in vacuo*, and the remaining oil dissolved in DCM (50 ml) and 0.5N $KHSO_4$ (50 ml). The organic phase was washed with 0.5N $KHSO_4$ (50 ml), 0.5M $NaHCO_3$ (3 x 50 ml), and brine (50 ml), dried with $MgSO_4$, filtered, and evaporated *in vacuo*. The remaining oil was purified by prep. HPLC (method A), to give compound 53C as an oil. Yield 70 mg (12 %).

^{1}H-NMR ($CDCl_3$): δ 1.5(s;9H); 2.1-2.35(m;4H); 2.65-3.05(m;2H); 3.45-3.8(m;2H); 4.75(t;1H); 5.05(m;1H); 5.9(broad t;1); 7.2-7.45(m;5H).

^{13}C-NMR ($CDCl_3$): δ 25.47; 28.72; 30.40; 39.93; 40.49; 46.42; 47,01; 74.11; 80.42; 83.32; 107.5; 118.66; 122.78; 122.87; 128.62; 128.76; 128.80; 132.05; 132.20; 155.25; 169.38.

Step D: (S)-1-(3-Amino-5-phenylpent-4-ynoyl)pyrrolidine-2-carbonitrile. TFA (53)

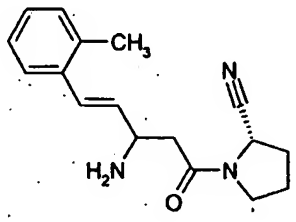
(S)-{1-[2-(2-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-phenylprop-2-ynyl}carbamic acid tert-butyl ester (0.070 g; 0.19 mmol) was dissolved in MeCN:H_2O (1:1) (4 ml). TFA (730µl, 9.5 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours, evaporated *in vacuo*, and purification by prep. HPLC (method A) to give the title compound. Yield: 55 mg (76 %).

^{1}H-NMR ($CDCl_3$):δ 1.9-2.2(m; 4H); 2.8-3.6(m; 4H); 4.7-4.9(m;2H); 7.2(m;3H); 7.4(d,d; 2H).

HPLC-MS (Method B): *m/z* = 268 (M + 1); Rt = 1.88 min. TIC Area : 100 %.

Example 54

1-(3-Amino-5-o-tolylpent-4-enoyl)-pyrrolidine-2-(S)carbonitrile. TFA (54)



Step A: 4-Vinyl-azetidin-2-one (54A)

Phenylsulfonylazetidin-2-one (6 g; 28 mmol) was dissolved in dry THF (100 ml). The reaction mixture was cooled to -78°C under N2. Vinylmagnesium bromide (1 M; 70 ml; 70 mmol) was added keeping the temperature below -60°C. The reaction mixture was stirred an additional 30 minutes at -78°C, then allowed to warm up slowly to 0°C. Stirring was continued for an additional 10 min. at 0°C, then for 30 min at room temperature. Saturated NH_4Cl(aq.) was added resulting in a white precipitate. The slurry was evaporated *in vacuo* to remove the THF. Water (200 ml) was added, and the product extracted with DCM (3 x 150 ml). The combined organic phase was dried (MgSO4), filtered, and evaporated *in vacuo* giving 3.16 g crude product, which was distilled in a Kugelrohr distiller (100°C; 0.06 mmHg) to give 1.69 g (62 %) of compound 54A as an oil.

^{1}H NMR ($CDCl_3$): δ: 6.39(br s; 1H); 5.93(ddd; J = 17.13; 10.23; 7.03Hz; 1H); 5.32(d; J = 16.82Hz; 1H); 5.20(d, J = 10.29Hz; 1H); 4.14(m; 1H); 3.22(ddd; J = 14.81; 5.15; 2.13Hz; 1H); 2.71(ddd; J = 14.81; 2.38; 1.38Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ: 167.80; 137.53; 117.05; 49.50; 45.07.

Step B: 4-[2-(2-Methylphenyl)-vinyl]-azetidin-2-one (54B)

Bis(tri-*t*-butylphosphin)palladium (26 mg; 0.05 mmol); 4-vinyl-azetidin-2-one (0.107 ml; 1.1 mmol); 2-iodotoluene (0.128 ml; 2.0 mmol) and TEA (0.280 ml; 2 mmol) were mixed in dry DMF under N_2 in a dry vial. The reaction mixture was shaken for 2 hours at 80°C., filtered, and evaporated *in vacuo*. The residue was purified on a silica gel column using ethyl acetate as eluent, to give compound 54B as white crystals. Yield 0.119 g (63 %). Mp: 95.8 - 96.5°C.

^{1}H NMR ($CDCl_3$): δ:7.43 (m; 1H); 7.18(m; 3H); 6.85(d; J = 15.56 Hz; 1H); 6.17(br s; 1H); 6.13((d,d; J = 15.56; 7.78Hz; 1H); 4.34(m; 1H); 3.31(ddd; J = 14.87; 5.21; 2.26 Hz; 1H); 2.83(ddd;J = 14.93; 2.51; 1.38 Hz; 1H); 2.34(s; 3H).

^{13}C-NMR ($CDCl_3$) δ: 167.58; 135.55; 134.94; 130.44; 130.20; 129.97; 128.05; 126.24; 125.72; 49.62; 45.59; 19.76.

HPLC-MS (method B): m/z = 188 (M + 1).

Step C: 2-Oxo-4-(2-o-tolylvinyl)azetidine-1-carboxylic acid tert-butyl ester (54C)

4-[2-(2-Methylphenyl)-vinyl]-azetidin-2-one (0.036 g; 0.19 mmol), Boc_2O ((0.050 g; 0.23 mmol), TEA (0.039; 0.39 mmol) and DMAP (5 mg) were mixed in DCM (10 ml) at RT for 144 hours. Water (10 ml) was added and the mixture extracted with DCM (2 x 10 ml). The organic phase was dried (MgSO4), filtered, and evaporated *in vacuo* to give compound 54C as a crude product, which was used in the subsequent step D without further purification. Yield 0.045 g.

Step D: {1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-o-tolylallyl}carbamic acid tert-butyl ester (54D)

2-Oxo-4-(2-o-tolylvinyl)azetidine-1-carboxylic acid tert-butyl ester (0.045 g; 0.16 mmol) was dissolved in DMF (10 ml). KCN (0.010 g; 0.16 mmol), 2-(S)-cyano-pyrrolidine.TFA (0.042 g; 0.20 mmol), and TEA (0.017 g; 0.17 mmol) were added. The reaction mixture was heated for 16 hours at 50°C, and evaporated *in vacuo*. The crude product was dissolved in water:DCM (1:1) (10 ml). The water phase was extracted with DCM (5 ml). The combined organic phase was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give compound 54D as a yellow oil, which was used in the subsequent step E without further purification. Yield 0.077 g.

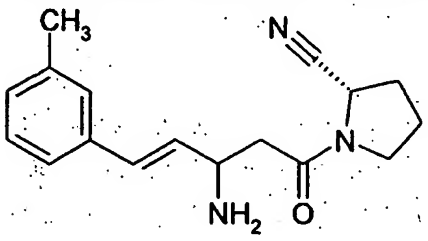
Step E: 1-(3-Amino-5-o-tolylpent-4-enoyl)pyrrolidine-2-(S)-carbonitrile (54)

{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-o-tolylallyl}carbamic acid tert-butyl ester (0.077 g) was added TFA (50 equivalents) in water:acetonitrile (1:1; 4 ml). The reaction mixture was stirred at RT for 96 hours, and evaporated *in vacuo*. The crude product was purified by preparative HPLC (method A) to give the title compound as the TFA salt. Yield: 0.040 g (50 %).

^{1}H NMR ($CDCl_3$): δ: 8.35 (s,br,2H); 7.4 (dd, 1H); 7.15 (dd, 3H); 7.0 (d,1H); 6.15 (q,1H); 4.7 (m,1H); 4.4 (m,1H); 3.65-3.25 (m, 2H); 3.1-2.6 (m,2H); 2.3 (s,3H); 2.15 (m, 4H).
HPLC-MS (method B): m/z = 284 (M + 1).

Example 55

1-(3-Amino-5-m-tolylpent-4-enoyl)pyrrolidine-2-(S)-carbonitrile (55)



Step A: 4-[2-(3-Methylphenyl)-vinyl]-azetidin-2-one (55A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol), 3-iodobenzene (0.218 ml; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 21 hours at 100°C, cooled, filtered, and evaporated *in vacuo*. The remaining oil was purified on a silica gel column using ethyl acetate as eluent to give compound 55A as a crystalline compound. Yield 0.134 g (72 %). Mp = 86.2 - 89.8°C.
^{1}H NMR ($CDCl_3$): δ: 7.26-7.07(m; 4H); 6.59(d; J = 15.82 Hz; 1H); 6.28(br s; 1H); 6.22(dd; J = 15.82; 7.78 Hz; 1H); 4.29(m; 1H); 3.28(ddd; J = 14.88; 5.27; 2.07Hz; 1H); 2.80 (ddd; 1H); 2.36(s; 3H).
^{13}C-NMR ($CDCl_3$) δ: 168.06; 138.68; 138.68; 136.20; 132.82; 128.97; 128.78; 128.06; 127.56; 124.06; 49.80; 45.88; 27.13.
HPLC-MS (method B): m/z = 188 (M + 1).

Step B: 2-Oxo-4-(2-m-tolylvinyl)azetidine-1-carboxylic acid tert-butyl ester (55B)

4-[2-(3-Methylphenyl)-vinyl]-2-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.123 g of compound 55B as a crude product.

Step C: {1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-m-tolylallyl}carbamic acid tert-butyl ester (55C)

2-Oxo-4-(2-m-tolylvinyl)azetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.195 g of compound 55C as a crude product.

Step D: 1-(3-Amino-5-m-tolyl-pent-4-enoyl)pyrrolidine-2-(S)-carbonitrile (55)

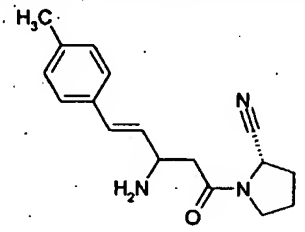
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-m-tolylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound, as the TFA salt. Yield 0.113 g (78 %).

^{1}H NMR ($CDCl_3$): δ: 8.2(s,br,2H); 7.15(s,br,4H); 6.7(dd,1H); 6.25(q,1H); 4.7(m,1H); 4.4(m,1H); 3.65-3.2(m,2H); 3.05-2.6(m,2H); 2.3(s,3H); 2.15(m,4H).

HPLC-MS (method B): *m/z* = 188 (M + 1).

Example 56

1-(3-Amino-5-p-tolyl-pent-4-enoyl)pyrrolidine-2-(S)-carbonitrile, TFA (56)



Step A: 4-[2-(4-Methylphenyl)-vinyl]-azetidin-2-one (56A))

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol); 4-methyliodobenzene (0.218 ml; 1.0 mmol) and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 21 hours at 100°C. The reaction mixture was filtered and evaporated *in vacuo*. The remaining oil was purified on a silica gel column using ethyl acetate as eluent giving compound 56A as a crystalline compound. Yield 0.140 g (75 %). Mp = 161.2 - 162.1°C.

^{1}H NMR ($CDCl_3$): δ: 7.27(d; 2H); 7.13 (d; 2H); 6.59(d; 1H); 6.34(s; 1H); 6.17(dd; J = 15.81; 7.53 Hz; 1H); 4.28(m; 1H); 3.27(ddd; J = 14.81; 5.15; 2.13Hz; 1H); 2.79 (ddd; J = 14.81; 2.51; 1.25 Hz; 1H); 2.34(s; 3H).

^{13}C-NMR ($CDCl_3$) δ: 168.20; 138.46; 133.48; 132.61; 129.77; 127.94; 126.79; 49.85; 45.87; 21.60.

HPLC-MS (method B): *m/z* = 188 (M + 1).

Step B: 2-Oxo-4-(2-p-tolylvinyl)azetidine-1-carboxylic acid tert-butyl ester (56B)

4-[2-(4-Methylphenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.150 g of compound 56B as a crude product.

Step C: {1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-p-tolylallyl}carbamic acid tert-butyl ester (56C)

2-Oxo-4-(2-p-tolylvinyl)azetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.158 g of compound 56C as a crude product.

Step D: 1-(3-Amino-5-p-tolyl-pent-4-enoyl)pyrrolidine-2-(S)-carbonitrile,TFA (56)

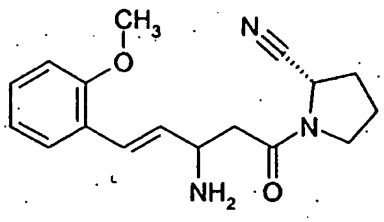
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-p-tolylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound as the TFA salt. Yield 0.090 g (55 %).

^{1}H NMR ($CDCl_3$): δ: 8.25 (s,br,2H); 7.25 (d,2H); 7.1(d,2H); 6.75 (dd,1H); 6.2 (q,1H); 4.7 (m,1H); 4.4 (m,1H); 3.6-3.2 (m, 2H); 3.1-2.6 (m, 2H); 2.35 (s,3H); 2.15 (d,br,4H);

HPLC-MS (method B): *m/z* = 188 (M + 1).

Example 57

1-[3-Amino-5-(2-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (57A)



Step A: 4-[2-(2-Methoxyphenyl)-vinyl]-azetidin-2-one (57)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol); 2-methoxyiodobenzene (0.234 ml; 1.0 mmol) and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 2 hours at 80°C, filtered, and evaporated *in vacuo* to give an oil, which was purified on a silica gel column using ethyl acetate as eluent to give compound 57A as a yellow oil. Yield 0.150 g (74 %).

^{1}H NMR ($CDCl_3$): δ: 6.897.41(m; 4H); 6.88(d; J = 15.81 Hz; 1H); 6.59(s; 1H); 6.24(dd; J = 15.81; 7.78 Hz; 1H); 4.28(m; 1H); 3.83(s; 3H); 3.25(ddd; J = 14.87; 5.08; 1.88Hz; 1H); 2.78(m; 1H).

^{13}C-NMR ($CDCl_3$) δ: 168.57; 157.12; 130.65; 129.71; 127.48; 125.26; 121.08; 114.65; 111.27; 55.78; 50.28; 45.74.

HPLC-MS (method B): m/z = 204 (M + 1).

Step B: 2-[2-(2-Methoxyphenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (57B)

4-[2-(2-Methoxyphenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.128 g of compound 57B as a crude product.

NNC 0072-0000-5320-1A Step C: [1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-(2-methoxyphenyl)allyl]carbamic acid tert-butyl ester (57C)

2-[2-(2-Methoxyphenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.179 g of compound 57C as a crude product.

Step D: 1-[3-Amino-5-(2-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (57)

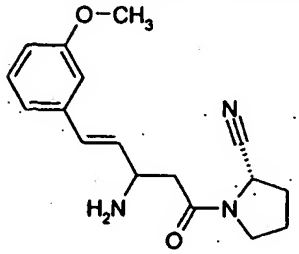
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-o-methoxyphenylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step D to give the title compound as the TFA salt. Yield 0.077g (57 %).

^{1}H NMR ($CDCl_3$): δ: 8.3(s,br,2H); 7.3(m,2H); 6.9(m,3H); 6.35(q,1H); 4.75(m,1H); 4.4(m,1H); 3.8(s,3H); 3.65-3.2(m,2H); 3.15-2.6(m,2H); 2.15(m,4H):

HPLC-MS (method B): m/z = 299 (M +), Rt = 1.96 min

Example 58

1-[3-Amino-5-(3-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (58)



Step A: 4-[2-(3-Methoxyphenyl)-vinyl]-azetidin-2-one (58A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol), 3-methoxyiodobenzene (0.233 g; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 2 hours at 80°C, filtered, and evaporated *in vacuo* to an oil which was purified on a silica gel column using ethyl acetate as eluent to give compound 58A as a crystalline compound. Mp = 89.5 - 90.1°C. Yield 0.131 g (65 %).

^{1}H NMR ($CDCl_3$): δ: 7.12(m; 1H); 6.89(m; 3H); 6.61(d; J = 15.81Hz; 1H); 6.23(dd; J = 15.81; 7.53Hz; 1H); 6.04(s; 1H); 4.31(m; 1H); 3.82(s; 3H); 3.31(ddd; J = 14.93; 5.15; 2.01Hz; 1H); 2.83(J = 14.93; 2.38; 1.51Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ:168.04; 160.23; 137.69; 132.60; 130.09; 129.32; 119.52; 114.12; 112.24; 55.62; 49.71; 45.88.

HPLC-MS (method B): m/z = 204 (M + 1).

2-[2-(3-Methoxyphenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (58B)

4-[2-(3-Methoxyphenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.040 g of compound 58B as a crude product.

Step C: [1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-(3-methoxyphenyl)allyl]carbamic acid tert-butyl ester (58C)

2-[2-(3-Methoxyphenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.070 g of compound 58C as a crude product.

Step E: 1-[3-Amino-5-(3-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (58)

{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-m-methoxyphenylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give

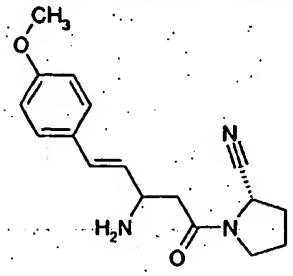
the title compound as the TFA salt. Yield 0.028 g (38 %).

^{1}H NMR ($CDCl_3$): δ: 8.3 (s,br,2H); 7.2 (d,1H); 6.9 (m,3H); 6.7 (dd,1H); 6.25(q,1H); 4.7(b,1H); 4.4(m,1H); 3.75(s,3H); 3.65-3.2(m,2H); 3.1-2.6(2H); 2.2 (m,4H).

HPLC-MS (method B): *m/z* = 300 (M + 1); Rf = 1.75 min

Example 59

1-[3-Amino-5-(4-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (59)



Step A: 4-[2-(4-Methoxyphenyl)-vinyl]-azetidin-2-one (59A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol); 3-methoxyiodobenzene (0.233 g; 1.0 mmol) and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 2 hours at 80°C, filtered, and evaporated *in vacuo* to give an oil, which was purified on a silica gel column using ethyl acetate as eluent to give compound 59A as a crystalline compound. Yield 0.122 g (60 %). Mp = 129.0 - 129.8°C.

^{1}H NMR ($CDCl_3$): δ: 7.29(d; J = 8.78 Hz; 2H); 6.86(J = 8.53 Hz; 2H); 6.56(d; J = 15.81Hz; 1H); 6.49(br s; 1H); 6.08(dd; J = 15.69; 7.66Hz; 1H); 4.26(m; 1H); 3.80(s; 3H); 3.26(ddd; J = 14.87; 5.21; 2.01Hz; 1H); 2.80(m; 1H).

^{13}C-NMR ($CDCl_3$) δ:168.34; 159.94; 132.13; 129.04; 128.11; 126.79; 114.47; 55.67; 49.90; 45.86.

Step B: 2-[2-(4-Methoxyphenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (59B)

4-[2-(4-Methoxyphenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.103 g of compound 59B as a crude product.

Step C: [1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-(4-methoxyphenyl)allyl]carbamic acid tert-butyl ester (59C)

2-[2-(4-Methoxyphenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.121 g of compound 59C as a crude product.

Step D: 1-[3-Amino-5-(4-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (59)

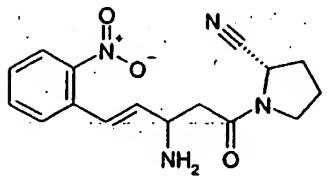
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-p-methoxyphenylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound as the TFA salt. Yield 0.086 g, (69 %).

^{1}H NMR ($CDCl_3$): δ 8.2(s,br,2H); 7.3(d,2H); 6.8(d,2H); 6.65(dd,1H); 6.1(q,1H); 4.7(m,1H); 4.35(m,1H); 3.8/s,3H); 3.65-3.2(m,2H); 3.15-2.6(m,2H); 2.1(d,br,4H).

HPLC-MS (method B): *m/z* = 300(M + 1); Rt = 1.82 min.

Example 60

1-[3-Amino-5-(2-nitrophenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (60)



Step A: 4-[2-(2-Nitrophenyl)-vinyl]-azetidin-2-one (60A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol), 2-iodonitrobenzene (0.249 g; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 2 hours at 80°C, filtered and evaporated *in vacuo*, to give an oil, which was purified on a silica gel column using DCM/MeOH (19:1) as eluent to give compound 60A as a yellow oil. Yield 0.074 g (34 %).

^{1}H NMR ($CDCl_3$): δ 7.97(d; J = 8.03Hz; 1H); 7.59(m; 2H); 7.45(m; 1H); 7.15(d; J = 15.81Hz; 1H); 6.23(dd; J = 15.69; 7.65Hz; 1H); 6.17(br s; 1H); 4.39(m; 1H); 3.36(ddd; J = 15.06; 5.27; 2.26Hz; 1H); 2.87(ddd; J = 14.87; 2.45; 1.25Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ: 168.04; 148.10; 134.37; 133.67; 132.09; 129.15; 129.02; 128.08; 125.03; 49.48; 45.69.

HPLC-MS (method B): *m/z* = 218 (M+).

Step B: 2-[2-(2-Nitrophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (60B)

4-[2-(2-Nitrophenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.094 g of compound 60B as a crude product.

Step C: [1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-(2-nitrophenyl)allyl]carbamic acid tert-butyl ester (60C)

2-[2-(2-Nitrophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.153 g of compound 60C as a crude product.

Step D: 1-[3-Amino-5-(2-nitrophenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (60)

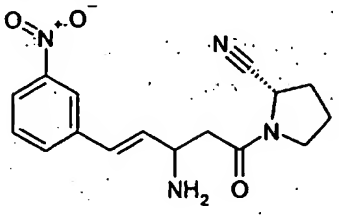
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-o-nitrophenylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound as the TFA salt. Yield 0.074 g (65 %).

^{1}H NMR (MeOH-d_4): δ 8.0(d,1H); 7.7(m,2H); 7.55(m,1H); 7.25(dd,1H); 6.3(m,1H); 4.8(t,1H); 4.45(m,1H); 3.8-3.45(m,2H); 3.15-2.7(m,2H); 2.4-2.0(m,4H).

HPLC-MS (method B): *m/z* = 315 (M + 1), Rt = 1.84 min.

Example 61

1-[3-Amino-5-(3-nitrophenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (61)



Step A: 4-[2-(3-Nitrophenyl)-vinyl]-azetidin-2-one (61A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol), 3-iodonitrobenzene (0.249 g; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and

heated for 2 hours at 80°C, filtered, and evaporated *in vacuo* to give an oil, which was purified on a silica gel column using DCM/MeOH (19:1) as eluent to give compound 61A as white crystals. Yield 0.050 g (23 %). Mp = 98.5 - 99.3°C

^{1}H NMR ($CDCl_3$): δ 8.23(s; 1H); 8.12(d; J = 8.03Hz; 1H); 7.69(d; J = 7.78Hz; 1H); 7.51(m; 1H); 6.72(d; J = 15.81Hz; 1H); 6.61(s; 1H); 6.43(dd; J = 15.81; 7.03Hz; 1H); 4.38(m; 1H); 3.36(ddd; J = 15.00; 5.21; 2.13Hz; 1H); 2.87(dd; J = 14.81; 1.51Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ: 168.10; 148.94; 138.08; 132.36; 130.20; 130.20; 130.04; 123.01; 121.46; 49.35; 45.83.

HPLC-MS (method B): m/z = 218 (M+).

Step B: 2-[2-(3-Nitrophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (61B)

4-[2-(3-Nitrophenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.067 g of compound 61B as a crude product.

Step C: [1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-(3-nitrophenyl)allyl]carbamic acid tert-butyl ester (61C)

2-[2-(3-Nitrophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.088 g of compound 61C as a crude product.

Step D: 1-[3-Amino-5-(3-nitrophenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (61)

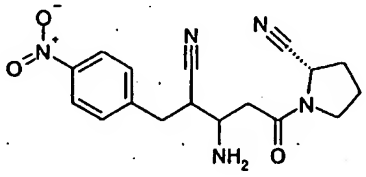
{1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-m-nitrophenylallyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound as the TFA salt. Yield 0.023 g (35 %).

^{1}H NMR (MeOH-d4): δ 8.35(s,1H); 8.2(d,1H); 7.85(d,1H); 7.6(t,1H); 6.95(d,1H); 6.5(m,1H); 4.85(m,1H); 4.45(m,1H); 3.75-3.5(m,2H); 3.1-2.8(m,2H); 2.4-2.1(M,4H).

HPLC-MS (method B): m/z = 315 (M + 1), Rt = 1.93

Example 62

1-[3-Amino-4-cyano-5-(4-nitro-phenyl)-pentanoyl]-pyrrolidine-2-(S)-carbonitrile; TFA (62)



Step A: 4-[2-(4-Nitrophenyl)-vinyl]-azetidin-2-one (62A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol), 4-iodonitrobenzene (0.249 g; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 2 hours at 80°C, filtered, and evaporated *in vacuo* to give an oil, which was purified on a silica gel column using DCM:MeOH (19:1) as eluent to give compound 62A as light yellow crystals. Yield 0.041 g (19 %). Mp = 127.4 - 128.9°C.

^{1}H NMR ($CDCl_3$): δ 8.19(d; J = 8.78Hz; 2H); 7.52(d; J = 8.78Hz; 2H); 6.73(d; J = 15.81Hz; 1H); 6.58(dd; J = 15.81; 7.03Hz; 1H); 4.38(m; 1H); 3.36(ddd; J = 14.81; 5.27; 2.26Hz; 1H); 2.86(dd; J = 14.81; 1.38Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ: 167.44; 147.24; 142.31; 133.55; 130.03; 127.12; 124.10; 48.99; 45.56.

Step B: 2-[2-(4-Nitrophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (62B)

4-[2-(4-Nitrophenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C to give 0.032 g of compound 62B as a crude product.

Step C: [2-Cyano-1-[2-(2-(S)-cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-3-(4-nitrophenyl)-propyl]-carbamic acid tert-butyl ester (62C)

2-[2-(4-Nitrophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.042 g of compound 62C as a crude "product". The expected product: [1-[2-(2-(S)-Cyanopyrrolidin-1-yl)-2-oxoethyl]-3-(4-nitrophenyl)allyl]carbamic acid tert-butyl ester was not detected, but further analysis in the next reaction step showed that surprisingly the cyanide anion group had added onto the double bond to give compound 62C.

Step D: 1-[3-Amino-4-cyano-5-(4-nitro-phenyl)-pentanoyl]-pyrrolidine-2-(S)-carbonitrile; TFA (62)

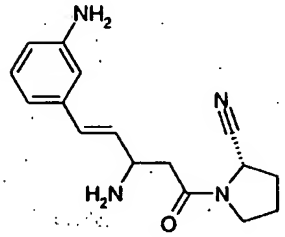
[2-Cyano-1-[2-(2-(S)-cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-3-(4-nitrophenyl)-propyl]-carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound as the TFA salt. Yield 0.011 g (24 %).

^{1}H NMR (MeOH-d4): δ 8.25(d,2H); 7.6(d,2H); 5.0(m,1H); 4.1-3.95(m,1H); 3.8-3.5(m,3H); 3.35-2.95(m,4H); 2.4-2.1(m,4H).

HPLC-MS (method B): *m/z* = 342 (M + 1), Rt = 1.92 min.

Example 63

1-[3-Amino-5-(3-amino-phenyl)-pent-4-enoyl]-pyrrolidine-2-carbonitrile; TFA (63)



Step A: 4-[2-(3-Amino-phenyl)-vinyl]-azetidin-2-one (63A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol), 3-iodoaniline (0.219 g; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 0.5 hours at 80°C, filtered, and evaporated *in vacuo*. The remaining oil was purified on a silica gel column using ethyl acetate as eluent to give compound 63A as an oil. Yield 0.048 g (25 %).

^{1}H NMR ($CDCl_3$): δ 7.12(m; 1H); 6.69(m; 3H); 6.54(d; *J* = 15.81Hz; 1H); 6.18(dd; 1H); 6.01(br s; 1H); 4.29(m; 1H); 3.69(br s; 2H); 3.29(ddd; *J* = 14.81; 5.21; 2.26Hz); 2.81(ddd; *J* = 14.81; 2.51; 1.51Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ: 168.28; 147.12; 137.35; 132.78; 129.98; 128.80; 117.42; 115.44; 113.27; 49.73; 45.79.

HPLC-MS (method B): *m/z* = 188 (M+).

Step B: 2-[2-(3-tert-Butoxycarbonylaminophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (63B)

4-[2-(3-Amino-phenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C, except for the use of 3 eq. of Boc_2O, to give 0.196 g of compound 63B as a crude product.

Step C: {3-[3-tert-Butoxycarbonylamino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxopent-1-enyl]phenyl}carbamic acid tert-butyl ester (63C)

2-[2-(3-tert-Butoxycarbonylaminophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.248 g of compound 63C as a crude product.

Step D: 1-[3-Amino-5-(3-amino-phenyl)-pent-4-enoyl]-pyrrolidine-2-carbonitrile, TFA (63)

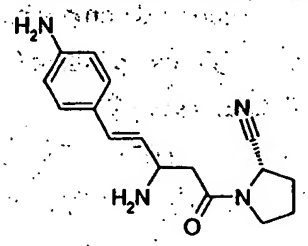
{3-[3-tert-Butoxycarbonylamino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxopent-1-enyl]phenyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step E to give the title compound as the TFA salt. Yield 0.071 g (42 %).

^1H NMR ($CDCl_3$): δ

HPLC-MS (method B): m/z = 285 (M + 1); Rt = 0.52 min.

Example 64

1-[3-Amino-5-(4-amino-phenyl)-pent-4-enoyl]-pyrrolidine-2-carbonitrile, TFA (64)



Step A: 4-[2-(4-Amino-phenyl)-vinyl]-azetidin-2-one (64A)

Bis(tri-t-butylphosphin)palladium (0.026 g; 0.05 mmol) was dissolved in dry DMF under N_2 at RT. 4-Vinyl-azetidin-2-one (0.107 ml; 1.1 mmol); 4-iodoaniline (0.219 g; 1.0 mmol), and TEA (0.28 ml; 2.0 mmol) were added. The reaction mixture was shaken and heated for 0.5 hour at 80°C, filtered and evaporated *in vacuo* to give an oil, which was

purified on a silica gel column using DCM:MeOH (19:1) as eluent to give compound 64A as yellow crystals. Yield 0.096 g (51 %). Mp = 143.1 - 144.4°C

^{1}H NMR ($CDCl_3$): δ: 7.17(d; J = 8.28Hz; 2H); 6.65(d; J = 8.28Hz; 2H); 6.52(d; J = 15.56Hz; 1H); 6.05(dd; J = 15.56; 7.53Hz; 1H); 4.24(m; 1H); 3.20(dd; J = 14.81; 5.02Hz; 1H); 2.69(dd; J = 14.81; 2.38Hz; 1H).

^{13}C-NMR ($CDCl_3$) δ: 171.32; 149.45; 133.89; 129.04; 127.96; 125.969; 116.68; 76.31; 45.75.

Step B: 2-[2-(4-tert-Butoxycarbonylaminophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester (64B)

4-[2-(4-Amino-phenyl)-vinyl]-azetidin-2-one was reacted and purified as described in example 54 step C, except for the use of 3 eq. of Boc_2O, to give 0.051 g of compound 64B as a crude product.

Step C: {4-[3-tert-Butoxycarbonylamino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxopent-1-enyl]phenyl}carbamic acid tert-butyl ester (64C)

2-[2-(4-tert-Butoxycarbonylaminophenyl)vinyl]-4-oxoazetidine-1-carboxylic acid tert-butyl ester was reacted and purified as described in example 54 step D to give 0.051 g of compound 64C as a crude product.

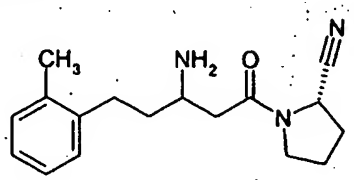
Step D: 1-[3-Amino-5-(4-amino-phenyl)-pent-4-enoyl]-pyrrolidine-2-carbonitrile, TFA (64)

{4-[3-tert-Butoxycarbonylamino-5-(2-(S)-cyanopyrrolidin-1-yl)-5-oxopent-1-enyl]phenyl}carbamic acid tert-butyl ester was reacted and purified as described in example 54 step C to give the title compound as the TFA salt. Yield 0.018 g (58 %).

^{1}H NMR ($CDCl_3$): δ:

HPLC-MS (method B): m/z = 285 (M + 1); Rt = 0.41min.

Example 65

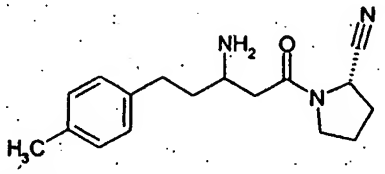


1-(3-Amino-5-o-tolyl-pentanoyl)-pyrrolidine-2-(S)-carbonitrile, TFA (65)

1-(3-Amino-5-o-tolylpent-4-enoyl)-pyrrolidine-2-(S)-carbonitrile. TFA (54) (0.040g; 0.101mmol) was dissolved in methanol (5 ml). Pd/C (5mg) was added and the reaction mixture was stirred vigorously under a hydrogen atmosphere for 30 min. The reaction mixture was filtered, evaporated, and purified by preparative HPLC (Method A) to give the title compound as the TFA salt. Yield 22mg (XX %) oil.

HPLC-MS (method B): *m/z* = 286 (M + 1); Rt = 1.94 min.

Example 66

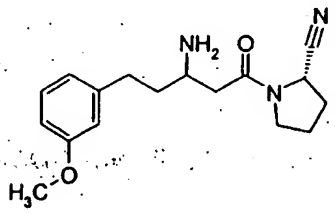


1-(3-Amino-5-p-tolyl-pentanoyl)-pyrrolidine-2-(S)-carbonitrile, TFA (66)

1-(3-Amino-5-p-tolyl-pent-4-enoyl)pyrrolidine-2-(S)-carbonitrile,TFA (56) (0.045g; 0.113mmol) was reacted and purified as described in example 65 to give the title compound as the TFA salt. Yield 12mg (XX %) oil.

HPLC-MS (method B): *m/z* = 286(M + 1); Rt = 1.99 min.

Example 67

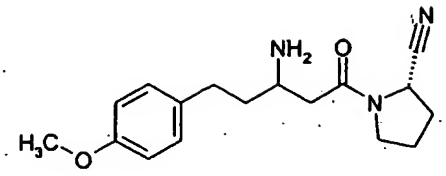


1-(3-Amino-5-(3-methoxyphenyl)-pentanoyl)-pyrrolidine-2-(S)-carbonitrile, TFA (67)

1-(3-Amino-5-(3-methoxyphenyl)-pent-4-enoyl)pyrrolidine-2-(S)-carbonitrile,TFA (58) (0.028g; 0.066mmol) was reacted and purified as described in example 65 to give the title compound as the TFA salt. Yield 17mg (XX %) oil.

HPLC-MS (method B): *m/z* = 302 (M + 1); Rt = 1.77 min.

Example 68



1-(3-Amino-5-(4-methoxyphenyl)-pentanoyl)-pyrrolidine-2-(S)-carbonitrile, TFA (68)

1-[3-Amino-5-(4-methoxyphenyl)pent-4-enoyl]pyrrolidine-2-(S)-carbonitrile, TFA (59) (0.050g; 0.120mmol) was reacted and purified as described in example 65 to give the title compound as the TFA salt. Yield 17mg (XX %) oil.

HPLC-MS (method B): *m/z* = 302 (M + 1); Rt = 1.72 min.

PHARMACOLOGICAL METHODS

Methods for measuring the activity of compounds which inhibit the enzymatic activity of CD26/DPP-IV

Summary.

Chemical compounds are tested for their ability to inhibit the enzyme activity of purified CD26/DPP-IV. Briefly, the activity of CD26/DPP-IV is measured *in vitro* by its ability to cleave the synthetic substrate Gly-Pro-p-nitroanilide (Gly-Pro-pNA). Cleavage of Gly-Pro-pNA by DPP-IV liberates the product p-nitroanilide (pNA), whose rate of appearance is directly proportional to the enzyme activity. Inhibition of the enzyme activity by specific enzyme inhibitors slows down the generation of pNA. Stronger interaction between an inhibitor and the enzyme results in a slower rate of generation of pNA. Thus, the degree of inhibition of the rate of accumulation of pNA is a direct measure of the strength of enzyme inhibition. The accumulation of pNA is measured spectrophotometrically. The inhibition constant, Ki, for each compound is determined by incubating fixed amounts of enzyme with several different concentrations of inhibitor and substrate.

Materials:

The following reagents and cells are commercially available:

Porcine CD26/DPP-IV (Sigma D-7052), Gly-Pro-pNA (Sigma G0513).

Assay buffer: 50 mM Tris pH 7.4, 150 mM NaCl, 0,1% Triton X-100.

Gly-Pro-pNA cleavage-assay for CD26:

The activity of purified CD26/DPP-IV is assayed in reactions containing:

70 µl assay buffer

10 µl inhibitor or buffer

10 µl substrate (Gly-Pro-pNA from a 0.1M stock solution in water) or buffer

10 µl enzyme or buffer

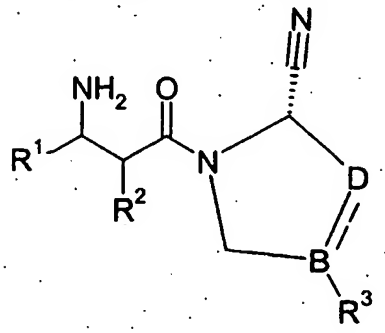
Reactions containing identical amounts of enzyme, but varying concentrations of inhibitor and substrate, or buffer as control, are set up in parallel in individual wells of a 96-well ELISA plate. The plate is incubated at 25 °C and absorbance is read at 405 nm after 60 min incubation. The inhibitor constants are calculated by non-linear regression hyperbolic fit and the result is expressed as inhibition constant (Ki) in nM.

Diabetes model

The Zucker Diabetic Fatty (ZDF) rat model can be used to investigate the effects of the compounds of the invention on both the treatment and prevention of diabetes as rats of this sub-strain are initially pre-diabetic although develop severe type 2 diabetes characterised by increased HbA1c levels over a period of 6 weeks. The same strain can be used to predict the clinical efficacy of other anti-diabetic drug types. For example, the model predicts the potency and limited clinical efficacy of thiazolidinedione insulin sensitizers compounds.

CLAIMS

1. A compound of formula I



Formula I

wherein

B and D are independently selected from carbon, nitrogen, oxygen, or sulphur.

The bond between B and D may be a single bond, and when one or both of B and D is not carbon, the bond connecting B and D may be a double bond.

R^1 is

- C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{2-15}-alkynyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, aryl-C_{2-10}-alkenyl, aryl-C_{2-10}-alkynyl, or heteroaryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8;

R^2 is hydrogen, C_{1-10}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, spiro-C_{3-10}-cycloalkyl, aryl-C_{1-10}-alkyl, -C(=O)-C_{1-10}-alkyl, -C(=O)-aryl, -C(=O)-heteroaryl, each optionally substituted with one or more substituents independently selected from R^4;

When R^2 is hydrogen R^1 may also be hydrogen;

R^3 is hydrogen, hydroxy, halogen, C_{1-10}-alkoxy, C_{1-10}-alkyl, aryl, aryloxy, aryl-C_{1-10}-alkoxy, heteroaryl, cyano, cyanoalkyl, and $COOR^2$;

R^4 is halogen, C_{1-5}-alkyl, nitro, hydroxy, CF_3, OCF_3, $OCHF_2$, perhalomethyl, perhaloethyl, cyano, phenyl, $COOR^5$, $CONR^5R^6$, $O(CO)R^5$, C_{1-10}-alkoxy, aryl-C_{1-10}-alkoxy, SR^5, SO_3R^5, NR^5R^6, $NHCOR^5$, or COR^5;

R^5 and R^6 are independently selected from hydrogen, C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, or aryl;

R^5 and R^6 together may form a C_{3-7}-alkylene bridge that optionally may be substituted with one or more R^7 independently;

R^7 is independently selected from cyano, halogen, hydroxy, C_{1-10}-alkyl, C_{1-10}-alkoxy, aryl, and heteroaryl;

R^8 is halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, perhalomethyl, perhaloethyl, cyano, phenyl, $COOR^9$, $CONR^{10}R^{11}$, $O(CO)R^9$, C_{1-10}-alkoxy, -C_{1-10}-alkyl-C(O)-R^9, -C_{1-10}-alkyl-C(O)-R^9, aryl-C_{1-10}-alkoxy, SR^9, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, SO_3R^9, $NR^{10}R^{11}$, $NHCOR^9$, or COR^9;

R^9 is C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{2-15}-alkynyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, aryl-C_{2-10}-alkenyl, heteroaryl-C_{1-10}-alkyl, C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12};

R^{10} and R^{11} are independently selected from hydrogen, C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, or aryl;

R^{12} is independently selected from halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, perhalomethyl, perhaloethyl, cyano, phenyl, COOH, $CONH_2$, C_{1-10}-alkoxy, aryl-C_{1-10}-alkoxy, SH, or NH_2;

R^1 and R^2 together may form a C_{3-7}-alkylene or C_{3-7}-alkenylene bridge to which is fused a phenyl or a heteroaryl ring;

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein B is carbon, nitrogen or sulphur.

3. A compound according to claim 2 wherein B is carbon or nitrogen.

4. A compound according to claim 3 wherein B is carbon.

5. A compound according to any one of the claims 1 to 4 wherein D is carbon, nitrogen or sulphur.

6. A compound according to claim 5 wherein D is carbon or nitrogen.

7. A compound according to claim 6 wherein D is carbon.

8. A compound according to any one of the claims 1 to 7 wherein R^1 is

- C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl, aryl-C_{1-10}-alkyl, aryl-C_{2-10}-alkenyl, or heteroaryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

9. A compound according to claim 8 wherein R^1 is

- C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, or aryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

10. A compound according to claim 9 wherein R^1 is

- C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1, heteroaryl, or ArG1-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

11. A compound according to claim 10 wherein R^1 is

- C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, heteroaryl, or ArG1-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4.
- C_{5-10}-cycloheteroalkyl or C_{5-10}-cycloheteroalkenyl each optionally substituted with one or more substituents independently selected from R^8.

12. A compound according to claim 11 wherein R^1 is C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4, or C_{5-10}-cycloheteroalkyl optionally substituted with one or more substituents independently selected from R^8.

13. A compound according to claim 12 wherein R^1 is cyclopentyl, cyclohexyl, cyclohexyl, bicyclo[2.2.1]heptyl, adamantyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-5-enyl, benzyl, phenethyl, each optionally substituted with one or more substituents independently selected from R^4, or pyrrolyl, piperidinyl, or hexahydroazepinyl, each optionally substituted with one or more substituents independently selected from R^8.

14. A compound according to claim 13 wherein R^1 is 3-piperidinyl or 4-piperidinyl each optionally substituted by R^8.

15. A compound according to claim 14 wherein R^1 is 3-piperidinyl or 4-piperidinyl each optionally substituted at the nitrogen atom by R^8.

16. A compound according to any one of the claims 8 to 11 wherein heteroaryl is Het1.

17. A compound according to any one of the claims 8 to 11 wherein heteroaryl is Het2.

18. A compound according to any one of the claims 8 to 11 wherein heteroaryl is Het3.

19. A compound according to any one of the claims 1 to 18 wherein R^2 is hydrogen, C_{1-10}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, aryl, heteroaryl, aryl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4.

20. A compound according to claim 19 wherein R^2 is hydrogen, C_{1-10}-alkyl, C_{3-10}-cycloalkyl, phenyl-C_{1-10}-alkyl, each optionally substituted with one or more substituents independently selected from R^4.

21. A compound according to claim 20 wherein R^2 is hydrogen.

22. A compound according to claim 1 wherein R^1 and R^2 together form a C_{3-7}-alkylene or C_{3-7}-alkenylene bridge to which is fused a phenyl ring.

23. A compound according to any one of the claims 1 to 21 wherein R^3 is hydrogen, hydroxy, halogen, C_{1-10}-alkoxy, C_{1-10}-alkyl, aryl, aryloxy, or aryl-C_{1-10}-alkoxy.

24. A compound according to claim 23 wherein R^3 is hydrogen, hydroxy, halogen, C_{1-10}-alkyl, or aryl-C_{1-10}-alkoxy.

25. A compound according to claim 24 wherein R^3 is hydrogen or aryl-C_{1-10}-alkoxy.

26. A compound according to claim 24 wherein R^3 is hydrogen.

27. A compound according to any one of the claims 1 to 26 wherein R^4 is halogen, C_{1-5}-alkyl, hydroxy, CF_3, OCF_3, $OCHF_2$, phenyl, $COOR^5$, $CONR^5R^6$, $O(CO)R^5$, C_{1-10}-alkoxy, aryl-C_{1-10}-alkoxy, NR^5R^6, or COR^5.

28. A compound according to claim 27 wherein R^4 is halogen, CF_3, C_{1-5}-alkyl, hydroxy, phenyl, $COOR^5$, $CONR^5R^6$, $O(CO)R^5$, NR^5R^6, or COR^5.

29. A compound according to claim 28 wherein R^4 is halogen, C_{1-5}-alkyl, $COOR^5$, $CONR^5R^6$, NR^5R^6, or COR^5.

30. A compound according to claim 28 wherein R^4 is halogen, C_{1-5}-alkyl, $COOR^5$, or $CONR^5R^6$.

31. A compound according to any one of the claims 1 to 30 wherein R^5 is hydrogen or C_{1-10}-alkyl.

32. A compound according to any one of the claims 1 to 31 wherein R^6 is hydrogen or C_{1-10}-alkyl.

33. A compound according to any one of the claims 1 to 30 wherein R^5 and R^6 together form a C_{3-6}-alkylene bridge optionally substituted with one or more R^7.

34. A compound according to any one of the claims 1 to 33 wherein R^7 is cyano, halogen, hydroxy, C_{1-10}-alkyl, or C_{1-10}-alkoxy.

35. A compound according to claim 34 wherein R^7 is cyano, halogen, hydroxy, or C_{1-10}-alkyl.

36. A compound according to claim 34 wherein R^7 is cyano or halogen.

37. A compound according to claim 34 wherein R^7 is cyano.

38. A compound according to any one of the claims 1 to 26 wherein R^8 is halogen, C_{1-5}-alkyl, nitro, hydroxy, OCF_3, $OCHF_2$, cyano, phenyl, $COOR^9$, $CONR^{10}R^{11}$, $O(CO)R^9$, C_{1-10}-alkoxy, -C_{1-10}-alkyl-C(O)-R^9, -C_{1-10}-alkyl-C(O)-R^9, SR^9, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, $NR^{10}R^{11}$, or COR^9.

39. A compound according to claim 38 wherein R^8 is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, $COOR^9$, $O(CO)R^9$, C_{1-10}-alkoxy, -C_{1-10}-alkyl-C(O)-R^9, -C_{1-10}-alkyl-C(O)-R^9, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, $NR^{10}R^{11}$, or COR^9.

40. A compound according to claim 39 wherein R^8 is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, $COOR^9$, $O(CO)R^9$, C_{1-10}-alkoxy, $S(O)_2R^9$, $S(O)_2NR^{10}R^{11}$, $NR^{10}R^{11}$, or COR^9.

41. A compound according to claim 39 wherein R^8 is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, $NR^{10}R^{11}$, or COR^9.

42. A compound according to any one of the claims 1 to 26 or 38 to 41 wherein R^9 is C_{1-15}-alkyl, C_{2-15}-alkenyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1, Het1, ArG1-C_{1-10}-alkyl, or C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12}.

43. A compound according to claim 42 wherein R^9 is C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, ArG1, or C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12}.

44. A compound according to claim 43 wherein R^9 is C_{1-15}-alkyl, C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, phenyl or C_{5-10}-cycloheteroalkyl, each optionally substituted with one or more substituents independently selected from R^{12}.

45. A compound according to any one of the claims 1 to 26 or 38 to 41 wherein R^{10} and R^{11} are independently selected from hydrogen, C_{1-10}-alkyl, or phenyl.

46. A compound according to claim 45 wherein R^{10} and R^{11} are independently selected from hydrogen or methyl.

47. A compound according to any one of the claims 1 to 26 or 38 to 44 wherein R^{12} is halogen, C_{1-5}-alkyl, hydroxy, OCF_3, $OCHF_2$, cyano, phenyl, COOH, $CONH_2$, C_{1-10}-alkoxy, SH, or NH_2.

48. A compound according to claim 47 wherein R^{12} is halogen, C_{1-5}-alkyl, hydroxy, cyano, phenyl, COOH, SH, or NH_2.

49. Use of a compound according to any one of the claims 1 to 48 as a pharmaceutical composition.

50. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 48 together with one or more pharmaceutically acceptable carriers or excipients.

51. A pharmaceutical composition according to claim 50 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 48.

52. A pharmaceutical composition according to claim 50 or 51 which furthermore comprises an inhibitor of neutral endopeptidase (NEP).

53. Use of a compound of the general formula (I) according to any one of the claims 1 to 48 or a diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of disorders and diseases in which an inhibition of DPP-IV has a beneficial effect.

54. Use of a compound as defined in claim 53 for the preparation of a pharmaceutical composition for the treatment of IGT.

55. Use of a compound as defined in claim 53 for the preparation of a pharmaceutical composition for the treatment of type 2 diabetes.

56. Use of a compound as defined in claim 53 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to type 2 diabetes.

57. Use of a compound as defined in claim 53 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

58. The use according to any one of the claims 53 to 57 wherein the pharmaceutical composition furthermore comprises an inhibitor of neutral endopeptidase (NEP).

59. A method for the treatment of disorders or diseases in which an inhibition of DPP-IV has a beneficial effect, the method comprising administering to a subject in need thereof an effective amount of a compound as defined in claim 53 or a pharmaceutical composition according to claim 50, 51 or 52.

60. The method according to claim 59 wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000232

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4025 C07D207/16 C07D409/06 C07D401/06 C07D405/06
C07D403/06 A61K31/40 A61P5/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/000180 A2 (MERCK & CO., INC., USA) 3 January 2003 (2003-01-03) scheme 7 page 16, line 5 - page 23, line 5 page 25, line 25 - page 26, line 17; claims; example 160	1-60
X	WO 01/55105 A1 (NOVO NORDISK A/S, DEN.) 2 August 2001 (2001-08-02) page 3, lines 9-20 page 24, line 10 - page 25, line 20; claims 4-8; compounds 39,40,42,43	1-60
Y	WO 98/19998 A (CIBA GEIGY AG ; VILLHAUER EDWIN BERNARD (US)) 14 May 1998 (1998-05-14) page 17 - page 22; claims	1-60

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2004	21/07/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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